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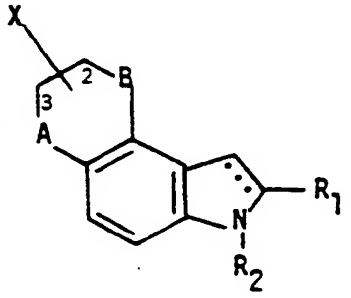
(54) Title: THERAPEUTICALLY USEFUL HETEROCYCLIC INDOLE COMPOUNDS



(I)

(57) Abstract

A therapeutically useful compound of formula (I) or pharmaceutically acceptable salts thereof where A and B are oxygen, sulfur or CH_2, X is an amine moiety as defined herein and R_1 and R_2 are as defined herein having $5HT_{1A}$ neuronal activity and/or dopamine receptor activity useful in the treatment of central nervous system and cardiovascular system disorders.

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THERAPEUTICALLY USEFUL HETEROCYCLIC INDOLE COMPOUNDS

BACKGROUND OF THE INVENTION

The present invention is related to new heterocyclic compounds containing both an indole and a 1,4-dioxan portion, processes for preparing such compounds, pharmaceutical preparation of such compounds and the use of such compounds in manufacture of a pharmaceutical preparation.

Psychiatric diseases are thought to be due to dysfunctions in monoaminergic neuronal systems, particularly those involving serotonin (5-HT) and dopamine (DA).

Anxiety is associated with increased activity in 5-HT systems. In animals where 5-HT has been depleted, benzodiazepine anxiolytics are not active in anti-anxiety assays that they otherwise are effective in. Seronotin neurons have autoreceptors that, when activated by agonists, depress firing rates of 5-HT cells. These receptors are of the 5-HT1A subtype. Because they depress 5-HT neuronal activity, it can be expected that 5-HT1A agonists will be anxiolytic.

Depression is a psychiatric condition thought to be associated with decreased 5-HT release. Most anti-depressants potentiate the effects of 5-HT by blocking the termination of activity through reuptake into nerve terminals. Since some 5-HT1A receptors are activated postsynaptically by 5-HT, 5HT1A agonists may also be anti-depressants. Since the postsynaptic 5-HT1A receptor may be less sensitive than the autoreceptor, high doses of 5-HT1A agonists, particularly very effective ones (i.e., those causing greater stimulation of the 5-HT1A receptor, a parameter referred to as "efficacy"), can be expected to be effective anti-depressants.

5-HT1A agonists are known to depress sympathetic nerve discharge and thus lower blood pressure. Thus, they may be useful in treating hypertension, congestive heart failure (by reducing cardiovascular afterload) and heart attack (be removing sympathetic drive to the heart). 5-HT1A agonists may also be useful in treating overeating and sexual dysfunction. These compounds have been shown to alter feeding and sexual behavior in animals.

Schizophrenia is thought to be due to hyperactivity in DA systems. Thus, currently available anti-psychotics are DA antagonists. Dopamine autoreceptors depress DA neuron firing rates, DA synthesis and release. Thus DA autoreceptor agonists can also be expected to be anti-psychotics. DA agonists are also useful for treating Parkinsonism, a disease caused by degeneration of DA neurons, and hyperprolactinemia,

since DA agonists depress prolactin release.

Dopamine autoreceptor antagonists are a new class of drug that increase release of DA by releasing the DA neuron from autoreceptor control. Thus, these drugs can be expected to be useful in conditions treatable with amphetamine and other similar stimulants which directly release DA. However, DA autoreceptor agonists will be much milder stimulants because, rather than directly releasing DA, they simply increase the release associated with the normal DA activity by releasing the cell from autoreceptor control. Thus, DA autoreceptor antagonists can be expected to be useful in treating overeating, attention deficit disorders, psychiatric, cognitive and motor retardation in demented and elderly patients, and in treating nausea and dizziness with space travel.

The compounds of the present invention have a variety of effects at 5-HT1A and DA receptors, and offer a variety of utilities associated with those activities.

Clinically, 5-HT1A agonists have also demonstrated anxiolytic properties. These compounds antagonize dopamine receptors at the same dose they stimulate 5-HT1A receptors.

The search for new CNS active compounds is focused on finding compounds with selective 5-HT1A receptor agonist effects without detrimentally influencing central dopamine receptors.

Drugs acting on central dopamine transmission are clinically effective in treating a variety of central nervous system disorders such as parkinsonism, schizophrenia, and mano-depressive illness. In parkinsonism, for example, the nigro-neostriatal hypofunction can be restored by an increase in postsynaptic dopamine receptor stimulation. In schizophrenia, the condition can be normalized by achieving a decrease in postsynaptic dopamine receptor stimulation. Classical anti-psychotic agents directly block the postsynaptic dopamine receptor. The same effect can be achieved by inhibition of intraneuronal presynaptic events essential for the maintenance of adequate neurotransmission, transport mechanism and transmitter synthesis.

In recent years a large body of pharmacological, biochemical and electrophysical evidence has provided considerable support in favor of the existence of a specific population of central autoregulatory dopamine receptors located in the dopaminergic neuron itself. These receptors are part of a homeostatic mechanism that modulates nerve impulse flow and transmitter synthesis and regulates the amount of dopamine released from the nerve endings.

Direct dopamine receptor agonists, like apomorphine, are able to activate the dopamine autoreceptors as well as the post synaptic dopamine receptors. The effects of autoreceptor stimulation appear to predominate when apomorphine is administered at low doses, whereas at higher doses the attenuation of dopamine transmission is outweighed by the enhancement of postsynaptic receptor stimulation. The anti-psychotic and anti-dyskinetic effects in man of low doses of apomorphine are likely due to the autoreceptor-stimulator properties of this dopamine receptor agonist. This body of knowledge indicates dopamine receptor stimulants with a high selectivity for central nervous dopamine autoreceptors would be valuable in treating psychiatric disorders.

INFORMATION DISCLOSURE STATEMENT

A tricyclic benzoquinoline compound has been described in EP 109 039 A by Yoshitomi Pharmaceutical Ind. KK which alleges antihypertensive activity.

A tricyclic indole containing compound is described in Chemical Abstract (CA 106(23):196345 entitled "Synthesis and pharmacological activity of 5,6- and 4,5-ethylendioxytryptamines; however, the structure lacks substitution on the dioxan ring and includes additional substitution on the indole.

U.S. Patent 4,510,157 describes another tricyclic structure containing an indole ring useful as dodpamine receptors, however, not with the same structural orientation.

Other heterocyclic dopamine receptors or alleged antidepressants having differently fused rings or structural arrangement are reported in EP 153 083 A by Eli Lilly & Co.; EP 23 761 by Smith Kline Corp; and a group of published applications by Marion Labs BE 827282-287.

SUMMARY OF THE INVENTION

The present invention is directed toward therapeutically useful compounds having the structural Formula I, as shown on the formula sheets below, or pharmaceutically acceptable salts thereof. Wherein, R_1 is hydrogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-CO_2R_2$, $-CONHR_2$, -CN, halogen, -CHO, $-(CH_2)_m-OR_2$, $-(CH_2)_m-Ar$, or $-SO_2R_2$;

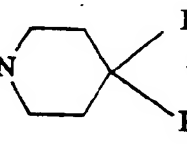
R_2 is hydrogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(CH_2)_m(C_3-C_8)$ cycloalkyl or cycloalkenyl, or $-(CH_2)_m-Ar$

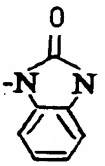
where Ar is phenyl, pyridyl, naphthyl, indolyl optionally substituted with one or more of the following:

$-OR_2$, halogen, -CN, -CHO, $-(CH_2)_m-Ph$, $-NO_2$, $-SR_2$ or NHR_2 and m is 0 to 6;

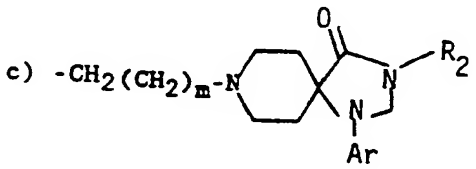
A and B are independently oxygen, CH_2 or sulfur;

X is a) $-CH_2(CH_2)_m-N(R_2)_2$,

b)  where R_3 is hydrogen, $-CO_2R_2$,

$-CONHR_2$, $-CN$, $-NHR_2$, $-CHO$, $-(CH_2)_m-Ar$, $-NR_2Ar$ or  ,

R_4 is hydrogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(CH_2)_m-(C_3-C_8)$ cycloalkyl or cycloalkenyl, $-(CH_2)_m-Ar$, $-CO_2R_2$, $-CONHR_2$, $-CN$ or $-CHO$, or

c) 

In another aspect the invention is directed toward a method for treating central nervous system and cardiovascular system disorders related to 5-HT1A neuronal activity or dopamine receptor activity comprising the administration of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. A typical dosage is from about 1-2000 mg orally or from about 0.1 to about 100 mg parenterally.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed toward pharmaceutical compounds as represented by structural Formula I (shown on Formula Sheet) or pharmaceutically acceptable salts thereof. These compounds exhibit 5-HT1A binding and dopamine receptor binding activity and therefore are useful in the therapeutic treatment of cardiovascular system and central nervous system disorders which are related to 5-HT1A and/or dopamine pathways.

In the definition of Formula I, the parenthetical term (C_a-C_b) is inclusive such that a compound of (C_1-C_8) would include compounds of one to eight carbons and their isomeric forms. The various carbon moieties are defined as follows: C_1-C_6 alkyl refers to an aliphatic hydrocarbon chain and includes branched or unbranched forms such as

methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, and isohexyl.

C_2-C_8 alkenyl refers to an aliphatic unsaturated hydrocarbons having a double bond and includes both branched and unbranched forms such as ethenyl, 1-methyl-1-ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-butenyl, 1-pentenyl, allyl, 3-pentenyl, 4-pentenyl, 1-methyl-4-pentenyl, 3-methyl-1-pentenyl, 3-methyl-allyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 1-methyl-4-hexenyl, 3-methyl-1-hexenyl, 3-methyl-2-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 1-methyl-4-heptenyl, 3-methyl-1-heptenyl, 3-methyl-2-heptenyl, 1-octenyl, 2-octenyl, or 3-octenyl. C_2-C_8 alkynyl refers to an aliphatic unsaturated hydrocarbon having a triple bond and includes both branched and unbranched forms. C_3-C_8 cycloalkyl refers to a saturated cyclic hydrocarbon such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl.

C_3-C_8 cycloalkenyl refers to an unsaturated cyclic hydrocarbon having a double bond.

Halogen is meant to include fluorine, chlorine, bromine and iodine.

Ar is meant to be phenyl, pyridyl, naphthyl and indole optionally substituted with one or more of OR_2, halogen, -CN, -CHO, $-(CH_2)_m$-Ph, $-NO_2$, $-SR_2$ or NHR_2 and m is 0 to 6;

Formula I may contain a saturated or unsaturated bond at the C_8-C_9 position which is represented by a solid and dotted line.

It will be apparent to those skilled in the art that compounds of this invention may contain chiral centers. The scope of this invention includes all enantiomeric or diastereomeric forms of Formula I compounds either in pure form or as mixtures of enantiomers or diastereomers. The therapeutic properties of the compounds may to a greater or lesser degree depend on the stereochemistry of a particular compound. Pure enantiomers as well as enantiomeric or diastereomeric mixtures are within the scope of the invention.

The compounds depicted in the Examples and Formula I Structure Sheets show A and B to be oxygen. Contemplated equivalents for oxygen are sulfur and CH_2.

Both organic and inorganic acids or bases can be employed to form non-toxic pharmaceutically acceptable salts of the compounds of this invention. Illustrative acids are sulfuric, nitric, phosphoric, hydrochloric, citric, acetic, lactic, tartaric, palmoic,

ethanedisulfonic, sulfamic, succinic, cyclohexylsulfamic, fumaric, maleic, and benzoic acid. Illustrative bases are sodium hydroxide, lithium hydroxide, and triethylamine. These salts are readily prepared by methods known in the art.

The compounds of this invention may be obtained by one of the following methods described below and outlined in the appropriate charts.

In clinical practice the compounds of the present invention will normally be administered in a therapeutically effective amount which is an amount sufficient to treat or cause observable modification of the cardiovascular or central nervous system disorder being treated. The compounds of Formula I can be administered orally, rectally, or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or as a pharmaceutically acceptable non-toxic acid addition salt, such as the hydrochloride, lactate, acetate, sulfamate salt, in association with a pharmaceutically acceptable carrier. The use and administration to a patient to be treated in the clinic would be readily apparent to a person of ordinary skill in the art.

In therapeutical treatment the suitable daily doses of the compounds of the invention are 1-2000 mg for oral application, preferentially 50-500 mg, and 0.1-100 mg for parenteral application, preferentially 0.5-50 mg.

Due to the influence of 5-HT1A receptor agonists on sympathetic nerve discharge, these compounds would be useful for treating hypertension, congestive heart failure, heart attack, and other disorders of the cardiovascular system.

The biological activity of these compounds indicates that they may be effective anxiolytic and anti-depressant agents. Other uses for these compounds include panic attacks, obsessive-compulsive disturbances, and senile dementia. In addition, central 5-HT receptor activation is believed to be involved in mediating sexual behavior. These compounds would be useful to stimulate sexual activity and to alleviate impotence.

The compounds of this invention are useful in the treatment of central nervous system disorders and cardiovascular system disorders as shown in physiological and biochemical tests. The methods are given as follows:

Binding: Inhibition of 3H-8-OH-DPAT binding in a bovine brain homogenate. Potency is given as nanomole (nM) dose required to inhibit 50% of DPAT binding (IC50). This test measures ability to bind to 5-hydroxytryptamine (HT1A) receptor.

For Dopamine (D_2): Inhibition of 3H-raclopride binding in rat striata homogenate. Potency is given as nm dose required to inhibit 50% of 3H-raclopride binding (IC_{50}).

This test measures the ability to bind to dopamine D_2 receptors.

Hypothermia: Starting with a dose of 30 mg/kg, four mice are injected subcutaneously with test compound. Twenty minutes later, the number of animals whose body temperature has decreased by 2°C. or more are counted. If all four animals reach criteria, the drug is considered "active", and subsequent readings are taken at 60 and 120 minutes after drug. The time for last statistically significant drug affect on mean body temperature is indicated in minutes. For all "active" compounds, doses are lowered by 0.5 log intervals until a dose which does not lower body temperature by 2°C. in any animal is found. Potency is given as mg/kg ED50 (dose required to depress temperature in two of four mice) as measured by Spearman-Karber statistics.

Biological binding and hypothermia data are shown in Table 1.

TABLE I

BIOLOGICAL DATA

Compound	$5HT_{1A}$ Binding IC_{50} (nM)	Hypothermia ED_{50} (mg/kg)	Dopamine D2-Receptor Binding IC_{50} (nM)
XIa	0.47	30.0	—
a'	29.20	—	3.20
a"	2.00	17.3	—
XIb	36.30	17.3	—
b'	24.70	30.0	52.20
XIc	0.29	—	—
XId	0.17	0.01	1.53
XIe	13.50	—	—
XIf	8.40	17.3	189.70
XIg	3.70	—	—
XIh	9.60	>30.0*	146.70
XIi	79.30	—	—
XIj*	4.00	1.3	54.60
XIk*	26.00	>30.0	349.90
XIl	2.30	—	—
XIm	1.00	—	0.13
XIn	267.90	—	—
XIo	279.90	—	97.30
XIp	11.00	—	—

a'position isomer of XIa

a" is the indoline derivative where C_7-C_8 bond is saturated

b' is the sodium salt of XIb

* hydrochloride salt form

Example 1: Preparation of 2,3-dihydro-2-((4-oxo-1-phenyl-1,3,8-triazaspiro(4.5)-dec-8-yl)methyl)-7H-1,4-dioxino(2,3-e)indol-8-methyl ester, XIa

The synthesis of Compound XI is represented in Chart I and is described below.

Step 1

Sodium hydride (50% oil dispersion - 5.28 g, 0.11 mol) was washed with hexane (3 x 20 mL) and dried under a stream of nitrogen. Dry dimethylsulfoxide (65mL) was added to the reaction flask and the resulting suspension was cooled to 0 C under a nitrogen atmosphere. To this suspension was added a solution of 2,3-dihydroxybenzaldehyde (13.81 g, 0.10 mol) in dimethylsulfoxide (35 mL + 10 mL rinse) in a slow stream via syringe. The external cooling was removed, and after stirring 1 hour at room temperature the near-black reaction mixture was treated with benzyl bromide (23.8 mL, 0.20 mol). The reaction gradually lightened in color and completely solidified in less than 1 hour. After one hour, the resulting material was physically broken-up and partitioned between ethyl acetate (2000 mL) and a 1:1 mixture of brine and water (500 mL total aqueous volume). The organic layer was washed with additional 50% brine (2 x 500 mL) and dried over anhydrous magnesium sulfate. After filtration and concentration in vacuo, the residue was chromatographed on 400 g of 230-400 mesh silica gel using 15-20% ethyl acetate/hexane to give 13.6 g of compound II. Recrystallization from ethyl acetate/hexane gave an iridescent, ivory-colored solid: Rf 0.44 (40% ethyl acetate/hexane); 1H NMR (300 MHz, CDCl3) 10.15 (s, 1 H, CHO), 7.5-7.1 (m, 8 H, aromatic H's), 6.05 (broad s, 1 H, O-H), 5.08 (s, 2 H, O-CH2); 13C NMR (75.5 MHz, CDCl3) 189.9, 149.8, 147.9, 135.8, 129.6, 129.1, 129.0, 128.7, 125.2, 122.1, 121.5, 78.5.

Step 2

A solution of II (26.78 g, 0.117 mol) in absolute ethanol (120 mL) was treated with 1.0 N aqueous sodium hydroxide (117 mL, 0.117 mol) and briefly heated to reflux under nitrogen (ca. 5 min). The black solution was cooled to room temperature and epichlorohydrin (92.6 mL, 1.16 mol) was added in a single portion. The solution was again brought to reflux using a preheated oil bath (110 C) and maintained at that temperature for an additional 30 minutes. After cooling to room temperature, the ethanol was removed in vacuo and the aqueous residue was diluted with water (650 mL) and extracted with ethyl acetate (3 x 350 mL). The combined organic layers were washed once with saturated aqueous sodium chloride (150 mL) and dried over anhydrous

magnesium sulfate. After filtration and concentration in vacuo, the residue was passed through a short column of silica gel using 40% ethyl acetate/hexane to remove polar, yellow material. The resulting product was dissolved in hot ether and cooled at 0 C over the weekend to give 26.12 g (78%) of compound III as a white solid, mp 62-63 C. The mother liquor (9.55 g of a yellow oil) was chromatographed on 600 g of 230-400 mesh silica gel using 20% ethyl acetate/hexane to give 5.93 g (18%) of additional III (total yield 96%): Rf 0.15 (20% ethyl acetate/hexane).

Step 3

A mixture of III (14.22 g, 50 mmol), cyclohexene (20.3 mL, 0.2 mol), and 10% palladium on carbon (1.40 g) in ethyl acetate (500 mL) was heated to reflux under nitrogen for 21 hour. After cooling to room temperature, the mixture was filtered through a pad of Celite, washing the filter cake well with ethyl acetate (220 mL). The filtrate was concentrated in vacuo, attempting to minimize exposure to air. The resulting residue was composed of a mixture of IV and V and was carried on directly to the final step.

Step 4

The unpurified product from the previous reaction was dissolved in ethanol (200 mL) and treated with triethylamine (14 mL, 0.10 mol) and water (200 mL). The solution was refluxed under nitrogen for 1 hour. After cooling to room temperature, the reaction mixture was directly concentrated in vacuo at 40 C on the rotary evaporator. The resulting yellow residue was chromatographed on 500 g of 230-400 mesh silica gel with 40% ethyl acetate/hexane to give 7.77 g (80%) of V as an off-white solid. Recrystallization from ethyl acetate/hexane provided the analytical sample, mp 70-71.5 C: Rf 0.15 (40% ethyl acetate/hexane).

Step 5

4-Dimethylaminopyridine (0.79 g, 6.50 mmol) was added in a single portion to a solution of V (971 mg, 5.00 mmol) and tert-butyldimethylsilyl chloride (0.90 g, 6.00 mmol) in dry dichloromethane (10 mL) at O°C under nitrogen. The cooling bath was removed and the solution was allowed to stir overnight at room temperature. The mixture, containing a white precipitate, was diluted with dichloromethane (100 mL), washed with water (50 mL) and saturated aqueous ammonium chloride (50 mL), then dried over anhydrous sodium sulfate. After filtration and concentration in vacuo, the resulting residue was chromatographed on 50 g of 230-400 mesh silica gel using 5%

ethyl acetate/hexane to give 1.30 g (84%) of VI as a colorless syrup which solidified on refrigeration, mp 32-33°C: R_f 0.26 (5% ethyl acetate/hexane).

Step 6

A solution of sodium methoxide in methanol (25 wt% - 19.1 mL, 83 mmol) was added fast dropwise over 5 minutes to a solution of VI (3.21 g, 10.4 mmol) and methyl azidoacetate (11.97 g, 104 mmol) in dry methanol (25 mL) at -22°C (carbon tetrachloride/dry-ice) under nitrogen. The temperature was raised to -5°C (mechanical cooling unit) and stirring was continued. After 30 minutes, additional methanol (10 mL - precooled) was added to thin the mixture, which had become quite thick and was foaming badly. After stirring overnight at -5°C, the dark reaction mixture was poured into ice-cold saturated aqueous ammonium chloride (110 mL) and extracted with ice-cold ethyl acetate (3 x 110 mL - it was necessary to wait out some difficult emulsions). The combined organic fractions were washed with ice-cold brine (1 x 55 mL) and dried over anhydrous sodium sulfate. After filtration and concentration in vacuo, the resulting residue (minus 8% removed for exploratory work) was adsorbed onto 15 g of 230-400 mesh silica gel (from a dichloromethane solution), then chromatographed on 300 g of 230-400 mesh silica gel using 2.5% ethyl acetate/hexane to give 2.81 g (72%) of VII as a yellow oil. The material solidified below room temperture; at room temperature the material was a semi-solid: R_f 0.25 (5% ethyl acetate/hexane). A solution of VII (16.5 g, 40.7 mmol) in o-xylene was refluxed (oil bath preheated to 180°C) under nitrogen for 1.5 hours. The solvent was removed in vacuo at 60°C to give a yellow solid residue which was recrystallized from hexane (aprox. 200 mL) to give 11.6 g (75%) of VIII as fine, white needles, mp 141.5-142.5°C: R_f 0.16 (10% ethyl acetate/hexane).

Step 7

A solution of VIII (3.78 g, 10.0 mmol) in dry tetrahydrofuran (35 mL) was treated with 1 M tetra-n-butylammonium fluoride in tetrahydrofuran (11.0 mL, 11.0 mmol) at room temperture under nitrogen. After stirring for 1 hour and 20 minutes, the cloudy mixture was poured into saturated aqueous ammonium chloride (115 mL) using methanol to aid in the transfer process. The organic solvents were removed in vacuo and the aqeous remainder was further diluted with water then extracted with ethyl acetate (3 x 70 mL). The combined organic layers were washed with brine (25 mL), then dried over anhydrous magnesium sulfate. After filtration and concentration, the resulting residue was chromatographed on 70 g of 230-400 mesh silica gel using 40% ethyl

acetate/hexane until IX began to elute, and then using 75% ethyl acetate/hexane to pick up the tailing. Thus was obtained 2.60 g (99%) of IX as a white solid, mp 158-160°C (from ethyl acetate/hexane): R_f 0.17 (40% ethyl acetate/hexane).

Step 8

p-Toluenesulfonyl chloride (660 mg, 3.46 mmol) was added in a single portion to a solution of IX (759 mg, 2.88 mmol) and 4-dimethylaminopyridine (457 mg, 3.74 mmol) in dry dichloromethane at 0°C under nitrogen. The cooling bath was removed and the solution was stirred overnight at room temperature. The white solid present after this time was collected and washed with a minimum amount of dichloromethane to give 960 mg (80%) of the compound X, mp 204-206°C (ethyl acetate/hexane).

Step 9

A mixture of X (3.17 g, 7.60 mmol), 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (5.27 g, 22.8 mmol), and powdered potassium carbonate (5.25 g, 38.0 mmol) in dry pyridine (75 mL) was heated at 75°C for 24 h under nitrogen. After cooling to room temperature, the black mixture was diluted with dichloromethane (1 vol.) and filtered through Celite. The black tar residing on top of the filter cake was washed/triturated with dichloromethane as well as possible. The residue obtained on concentration of the filtrate in vacuo was taken up in a large volume of dichloromethane and chromatographed on 300 g of 230-400 mesh silica gel using 75% ethyl acetate/hexane (a fair amount of undissolved XIa may have simply been deposited at the head of the column) to give 2.01 g (56%) of XIa as a pale yellow, beige solid. (The yellow coloration was easily removed on trituration with most organic solvents) Recrystallization from methanol (a large volume of methanol is required, then reduction of the volume by one-half until precipitation is evident on the hot plate) gave an off-white solid with vague melting point: R_f 0.18 (75% ethyl acetae/hexane); IR (mull) 3320, 2954, 2924, 2856, 1714, 1690, 1529, 1259, 1237, 1217 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) 11.85 (broad s, 1 H, indole N-H), 8.66 (broad s, 1 H, lactam N-H), 7.25 (t, J = 7.6 Hz, 2 H, phenyl meta H's), 7.00 (d, J = 2.0 Hz, 1 H, vinylic H), 6.95 (m, 4 H, phenyl ortho H's & aromatic H's), 4.58 (s, 2 H, N-CH_2-N), 4.49 (m, 1 H, O-CH), 4.36 (m, 1 H, O-CH_2a), 4.05 (dd, J = 11.5 Hz, J = 6.7 Hz, 1 H, O-CH_2b), 3.85 (s, 3 H, O-CH_3), 3.0-2.5 (m, 8 H, N-CH_2's & N-C-CH_2a's), 1.60 (m, 2 H, N-C-CH_2b's); ^{13}C NMR (300 MHz, DMSO-d6) 177.2, 162.4, 144.3, 135.9 (overlap), 134.8, 129.9, 127.5, 119.1, 118.5, 117.6, 115.1, 106.0, 104.6, 72.5, 67.2, 59.6, 58.8, 58.5, 52.6, 51.4 & 50.5

(differentiation of the piperidine-ring carbons alpha to the nitrogen), 29.4; HRMS, m/e 476.2076 ($C_26H_28N_4O_5$ requires 476.2060); Anal. Calcd for $C_26H_28N_4O_5$ 0.5 CH_3OH: C, 64.62; H, 6.14; N, 11.38. Found: C, 64.85; H, 5.98; N, 11.27.

The preparation of Examples 2-6 are structurally represented on Chart II for Compounds XIb through XIf.

Example 2: Preparation of 7H,4-Dioxino(2,3-e)indole-8-carboxylic acid, 2,3-dihydro-2-((4-oxo-1-phenyl-1,3,8-triazaspiro(4.5)dec-8-yl), XIb

A suspension of **XIa** as prepared in Example 1 (200 mg, 0.40 mmol) in methanol (2 mL) was treated with a solution of lithium hydroxide monohydrate (34 mg, 0.80 mmol) in water (1 mL). The heterogeneous mixture was heated under nitrogen at 60°C for 4.5 hours during which time a clear amber solution was gradually obtained. After cooling to room temperature, the solution was diluted with water (6 mL) and acidified to pH 7 with aqueous 1 N hydrochloric acid. The voluminous white solid which precipitated was filtered only with great difficulty - it was subsequently determined that a more manageable solid results if the methanol is first removed in vacuo. The total amount of material was redissolved using aqueous acetone. After concentration in vacuo, the residue was triturated with water to extract-out the inorganic salts and the resulting off-white solid was filtered and washed with water. Recrystallization of this material was not possible and so the product was purified by reprecipitation: a suspension in water was treated with aqueous 1 N sodium hydroxide until a clear solution was obtained (pH 12), then the pH was adjusted to 7 with aqueous 1 N hydrochloric acid. The resulting solid was filtered, washed with water, and air-dried on the filter funnel for a considerable time before it could be manipulated to give 145 mg (actual yield greater than 90%) of **XIb** as a beige powder (decomposes at approx. 230°C with gas evolution): R_f 0.20 (100:50:5 chloroform/methanol/concentrated aqueous ammonium hydroxide); ^1H NMR (300 MHz, DMSO-d6) 11.59 (broad s, 1 H, indole N-H), 8.70 (broad s, 1 H, CON-H), 7.22 (t, J = 7.7 Hz, 2 H, Ph meta H's), 6.89 (m, 5 H, Ph ortho H's & vinylic H & aromatic H's), 6.73 (t, J = 7.2 Hz, 1 H, Ph para H), 4.59 (s, 2 H, N-CH_2-N), 4.55 (m, 1 H, O-CH), 4.36 (broad d, J = 10.3 Hz, 1 H, O-CH_2a), 4.05 (dd, J = 11.2 Hz, J = 6.7 Hz, 1 H, O-CH_2b), 3.1-2.55 (m, 8 H, N-CH_2's & N-C-CH_2a's), 1.63 (m, 2 H, N-C-CH_2b's); ^{13}C NMR (75.5 MHz, DMSO-d6) 176.2, 163.0, 143.3, 134.8, 133.5, 129.0, 118.3, 117.6, 115.8, 114.2, 105.0, 102.9, 71.3, 66.2, 58.7, 57.9, 57.5, 50.3, 49.5, 28.2; HRMS (FAB), m/e 463.1987 [$C_25H_27N_4O_5$ (M + 1)

requires 463.1981]; Anal. Calcd for $C_25H_26N_4O5$ 1.25 H_2O: C, 61.91; H, 5.92; N, 11.55. Found: C, 61.90; H, 5.88; N, 11.54.

Example 3: Preparation of 7H-1,4-Dioxino(2,3-e)indole-8-carboxamide, 2,3-dihydro-2-((4-oxo-1-phenyl-1,3,8-triazaspiro(4.5)dec-8-yl)methyl)-, **XIc**

A suspension of **XIa** (1.00g, 1.92 mmol) and sodium cyanide (10 mg, 0.20 mmol) in 16% methanolic ammonia (100 mL) was heated in a pressure tube (Ace #15 thread) for 5 days at 100°C. The dark homogeneous mixture was cooled and concentrated in vacuo. The residue was taken-up in dichloromethane plus the minimum amount of methanol and chromatographed on 50 g of 230-400 mesh silica gel using 75% ethyl acetate/hexane until a small amount of unreacted **XIa** was recovered, followed by 2% methanol/ethyl acetate to give a pale-yellow solid. Recrystallization from methanol gave 473 mg (53%) of **XIc** as a white solid; crystallization of the mother liquor from ethyl acetate gave an addtional 85 mg of **XIc** as a beige solid: R_f 0.16 (1% methanol/ethyl acetate); IR (mull) 2953, 2925, 2867, 2855, 1706, 1676, 1599, 1515, 1501, 1373 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) 11.41 (broad s, 1 H, indole N-H), 8.66 (broad s, 1 H, CON-H), 7.91 (broad s, 1 H, NH_2a), 7.26 (broad s, 1 H, NH_2b), 7.25 (t, J = 7.4 Hz, 2 H, meta phenyl H's), 7.10 (d, J = 1.7 Hz, 1 H, vinyl H), 6.87 (m, 3 H, ortho phenyl H's & aromatic H), 6.76 (m, 2 H, para phenyl H & aromatic H), 4.58 (s, 2 H, N-CH_2-N), 4.45 (m, 1 H, O-CH), 4.38 (m, 1 H, O-CH_2a), 4.04 (m, 1 H, O-CH_2b), 3.05-2.5 (m, 8 H, N-CH_2's & N-C-CH_2a's), 1.58 (m, 2 H, N-C-CH_2b's); ^13C NMR (75.5 MHz, DMSO-d6) 176.2, 162.6, 143.3, 134.9, 134.7, 132.9, 131.3, 129.0, 118.3, 117.6, 114.8, 114.3, 104.8, 99.6, 71.7, 66.3, 58.6, 57.9, 50.6, 49.6, 28.4; HRMS, m/e 461.2074 ($C_25H_27N_5O_4$ requires 461.2063); Anal. Calcd for $C_25H_27N_5O_4$ 0.5 EtOAc: C, 64.15; H, 6.18; N, 13.85. Found: C, 63.84; H, 6.46; N, 13.98.

Example 4: Preparation of 7H-1,4-Dioxino(2,3-e)indole-8-carbonitrile, 2,3-dihydro-2-((4-oxo-1-phenyl-1,3,8-triazaspiro(4.5)dec-8-yl)methyl)-, **XId**

A solution of **XIc** (61 mg, 0.121 mmol) in dry tetrahydrofuran (4 mL) under nitrogen at room temperature was treated with the inner salt of methyl (carboxysulfamoyl)triethylammonium hydroxide (Burgess reagent) (32 mg, 0.133 mmol). After stirring 1 hour, a second portion of Burgess reagent (32 mg, 0.133 mmol) was added and stiiring was continued for an additional hour. The mixture was concentrated in vacuo and the residue was chromatographed on 5 g of 230-400 mesh silica gel using 3.5% methanol/dichloromethane to give 51 mg (94%) of **XId** as a white solid. The material could

not be successfully recrystallized, and yielded the most workable solid upon concentration in vacuo from its toluene solution: R_f 0.35 (5% methanol/dichloromethane); IR (mull) 2953, 2922, 2867, 2855, 1707, 1519, 1503, 1457, 1373, 1242, & 2221 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 9.33 (broad s, 1 H, N-H), 7.24 (m, 3 H, meta phenyl H's & CON-H), 7.05 (d, J = 1.4 Hz, 1 H, vinylic H), 6.97 (d, J = 8.8 Hz, 1 H, aromatic H), 6.86 (m, 4 H, ortho phenyl H's & aromatic H & para phenyl H), 4.74 (s, 2 H, N-CH_2-N), 4.52 (m, 1 H, O-CH), 4.40 (dd, J = 11.4 Hz, J = 2.2 Hz, 1 H, O-CH_2a), 4.09 (dd, J = 11.4 Hz, J = 6.8 Hz, 1 H, O-CH_2b), 3.2-2.6 (m, 8 H, N-CH_2's & N-C-CH_2a's), 1.78 (m, 2 H, N-C-CH_2b's); ^{13}C NMR (75.5 MHz, $CDCl_3$) 177.9, 142.9, 136.2 (possible overlap), 135.3, 133.2 (possible overlap), 129.2, 119.1, 117.9, 115.5, 114.3. 110.6, 105.5, 104.0, 71.9, 66.9, 59.2, 59.0, 58.3, 50.8, 49.9, 29.1, 29.0; HRMS, m/e 443.1964 ($C_25H_25N_5O_3$ requires 443.1957).

Example 5: Preparation of 7H-1,4-Dioxino(2,3-e)indole-8-carboxylic acid, 2,3-dihydro-2-((4-oxo-1-phenyl-1,3,8-triazaspiro(4.5)dec-8-yl)methyl)-,butyl ester, XIe

A suspension of XIa (95 mg, 0.200 mmol) and 1,8 -diazabicyclo[5.4.0]undec-7-ene (3 mg, 0.020 mmol) in dry 1-butanol (volume varied from 2-8 mL on draining of the Soxhlet) was refluxed under nitrogen using a Soxhlet extractor containing 3 A molecular sieves (1.8 g) in a cellulose thimble. After 31 h, refluxing was stopped and the solution was allowed to stand overnight at room temperature. The 1-butanol was removed in vacuo and the solid residue was dissolved in dichloromethane (approx. 15 mL) and chromatographed on 10 g of 230-400 mesh silica gel using 75% ethyl acetate/hexane to give a white solid (105 mg). The solid was recrystallized from ethyl acetate to give 79 mg (76%) of XIe as very fine, white needles, mp 203.5 - 204.5°C: R_f 0.21 (75% ethyl acetate/hexane); IR (mull) 3322, 2953, 2926, 2863, 2854, 1717, 1695, 1253, 1207, 770 cm-1; 1H NMR (300 MHz, DMSO-d6) 11.79 (broad s, 1 H, indole N-H), 8.66 (broad s, 1 H, amide N-H), 7.24 (t, J = 7.3 Hz, 2 H, phenyl meta H's), 6.99 (s, 1 H, vinylic H), 6.95-6.75 (m, 4 H, aromatic H's & phenyl ortho H's), 6.75 (t, J = 7.3 Hz, 1 H, phenyl para H), 4.59 (s, 2 H, N-CH_2-N), 4.5-4.35 (m, 2 H, O-CH & O-CH_2a), 4.28 (t, J = 6.3 Hz, 2 H, butyl O-CH_2), 4.04 (dd, J = 11.0 Hz, J = 6.7 Hz, 1 H, O-CH_2b), 3.0-2.5 (m, 8 H, N-CH_2's & N-C-CH_2a's), 1.75-1.35 (m, 6 H, N-C-CH_2b's & CH_2's), 0.94 (t, J = 7.2 Hz, 3 H, CH_3); 13C NMR (75.5 MHz, DMSO-d6) 178.0, 162.9, 145.1, 136.8, 135.6, 130.7, 128.6, 119.9, 119.3, 118.3,

115.9, 106.8, 105.3, 73.3, 68.1, 65.7, 60.4, 59.7, 59.4, 52.2, 51.4, 32.1, 30.2, 20.4, 15.3; HRMS, m/e 518.2542 ($C_29H_34N_4O_5$ requires 518.2529); Anal. Calcd for $C_29H_34N_4O_5$: C, 67.16; H, 6.61; N, 10.80. Found: C, 67.08; H, 6.76; N, 10.83.

Example 6: Preparation of 7H-1,4-Dioxino(2,3-e)indole-8-carboxylic acid, 2,3-dihydro-2-((4-oxo-1-phenyl-1,3,8-triazaspiro(4.5)dec-8-yl)methyl)-, phenylmethyl ester, **XIf**

A suspension of **XIa** (95 mg, 0.200 mmol) and 1,8 -diazabicyclo[5.4.0]undec-7-ene (3 mg, 0.020 mmol) in dry benzyl alcohol (2 mL) and toluene (volume varied from 1-7 mL on draining of the Soxhlet) was refluxed under nitrogen overnight using a Soxhlet extractor containing 3 A molecular sieves (1.8 g) in a cellulose thimble. The toluene and the benzyl alcohol were removed in vacuo (the alcohol required Kugelrohr distillation at 90°C/0.1 mmHg), and the residue, applied in dichloromethane, was chromatographed on 10 g of 230-400 mesh silica gel using 75% ethyl acetate/hexane to give a white solid (105 mg). The solid was recrystallized from acetone to give 68 mg (61%) of **XIf** as very fine, white needles, mp 217-219°C: R_f 0.19 (75% ethyl acetate/hexane); IR (mull) 3350, 2954, 2924, 2855, 1717, 1710, 1701, 1253, 1212, 1198 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) 11.86 (broad s, 1 H, indole N-H), 8.66 (broad s, 1 H, amide N-H), 7.5-7.3 (m, 5 H, benzyl Ph H's), 7.23 (t, J = 7.1 Hz, 2 H, meta phenyl H's), 7.05 (s, 1 H, vinylic H), 6.95-6.8 (m, 4 H, ortho phenyl H's & aromatic H's), 6.73 (t, J = 7.2 Hz, 1 H, para phenyl H), 5.37 (s, 2 H, Ph-CH_2), 4.58 (s, 2 H, N-CH_2-N), 4.47 (m, 1 H, O-CH), 4.37 (m, 1 H, O-CH_2a), 4.05 (m, 1 H, O-CH_2b), 3.0-2.45 (m, 8 H, N-CH_2's & N-C-CH_2a's), 1.57 (m, 2 H, N-C-CH_2b's); ^13C NMR (75.5 MHz, DMSO-d6) 178.0, 162.6, 145.1, 137.9, 136.8, 135.7, 130.7, 130.2, 129.8, 129.7, 128.3, 120.0, 119.3, 118.5, 115.9, 106.8, 105.8, 73.7, 68.1, 67.4, 60.4, 59.7, 59.4, 52.2, 51.4, 30.2; HRMS, m/e 552.2377 ($C_32H_32N_4O_5$ requires 552.2373); Anal. Calcd for $C_32H_32N_4O_5$: C, 69.55; H, 5.84; N, 10.14. Found: C, 69.25; H, 5.92; N, 10.11.

Examples 7-11 are structurally represented in Chart III for compounds XIg-k.

Example 7: Preparation of 7H-1,4-Dioxino(2,3-e)indole-8-carboxylic acid, 2-((4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl)methyl)-2,3-dihydro-, methyl ester, monohydrochloride, **XIg**

A solution of **X** (125 mg, 0.300 mmol), 4-(2-keto-1-benzimidazolinyl)-piperidine (196 mg, 0.900 mmol), and powdered, anhydrous potassium carbonate (207 mg, 1.50

mmol) in dry pyridine (3 mL) was stirred under nitrogen at 75°C for 24 h. After cooling to room temperature, the black mixture was diluted with dichloromethane and filtered through non-absorbent cotton. The filtrate was concentrated in vacuo, allowing a small amount of pyridine to remain. The residue was taken-up in a large volume of dichloromethane and chromatographed on 9 g of 230-400 mesh silica gel using 100% ethyl acetate to give 63 mg (45%) of **XIg** as a light-yellow solid: R_f 0.15 (100% ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d6) 11.87 (broad s, 1 H, amide N-H), 10.88 (broad s, 1 H, indole N-H), 7.3-6.8 (m, 7 H, aromatic H's & vinylic H), 4.50 (m, 1 H, O-CH), 4.37 (d, J = 10.7 Hz, O-CH_2a), 4.18 (m, 1 H, N-CH), 4.05 (dd, J = 11.4 Hz, J = 6.8 Hz, 1 H, O-CH_2b), 3.86 (s, 3 H, O-CH_3), 3.18 (broad d, J = 10.0 Hz, 1 H, O-C-CH2a-N), 3.04 (broad d, J = 8.1 Hz, 1 H, O-C-CH_2b-N), 2.72 (broad d, J = 5.6 Hz, 2 H, N-CH_2a's), 2.55-2.2 (m, 4 H, N-CH_2b's & N-C-CH_2a's), 1.64 (m, 2 H, N-C-CH_2b's); 13N NMR (75.5 MHz, DMSO-d6) 163.2, 155.5, 136.8, 135.6, 130.9, 130.1, 128.4, 122.2, 122.1, 119.9, 118.4, 110.5, 110.4, 106.8, 105.5, 73.5, 68.0, 59.2, 55.7, 54.6, 53.4, 51.7, 30.5, 30.4. The hydrochloride salt was prepared by treating a suspension of **XIg** in methanol with 40% methanolic hydrogen chloride. The salt precipitated as a pale yellow solid, mp approx. 300°C (dec): HRMS, m/e 462.1915 ($C_25H_26N_4O_5$ requires 462.1903); Anal. Calcd for $C_25H_26N_4O_5$ HCl 0.5 MeOH: C, 59.47; H, 5.68; N, 10.88. Found: C, 59.49; H, 5.75; N, 10.98.

Example 8: Preparation of 7H-1,4-Dioxino(2,3-e)indole-8-carboxylic acid, 2-((4-(ethoxycarbonyl-1-piperidinyl)methyl)-2,3-dihydro-, methyl ester, monohydrochloride, **XIh**

A solution of **X** (291 mg, 0.700 mmol), ethyl isonipecotate (329 mg, 2.10 mmol), and powdered, anhydrous potassium carbonate (482 mg, 3.50 mmol) in dry pyridine (7 mL) was stirred overnight under nitrogen at 75°C. After cooling to room temperature, the black mixture was concentrated in vacuo and the residue was taken-up in water (50 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (10 mL), then dried over anhydrous sodium sulfate. After filtration and concentration, the residue (applied in dichloromethane) was chromatographed on 20 g of 230-400 mesh silica gel using 40% ethyl acetate/hexane to give, Secondly was isolated 150 mg (53%) of **XIh** also as a beige solid, mp 153-154.5°C (benzene). Treatment of this material with methanolic hydrogen chloride provided the hydrochloride salt as a white solid after recrystallization from methanol/ethyl acetate. For the free-

base: R_f 0.17 (40% ethyl acetate/hexane); IR (mull) 3341, 2954, 2925, 2855, 1735, 1687, 1528, 1446, 1257, 1217 cm_{-1}; ^1H NMR (300 MHz, $CDCl_3$) 9.34 (broad s, 1 H, N-H), 7.21 (m, 1 H, vinylic H), 6.90 (m, 2 H, aromatic H's), 4.43 (m, 1 H, O-CH), 4.32 (d, J = 11.3 Hz, 1 H, O-$CH2_a$), 4.14 (quart, J = 7.2 Hz, 2 H, ethyl O-CH_2), 4.03 (dd, J = 11.3 Hz, J = 6.9 Hz, 1 H, O-CH_2b), 3.93 (s, 3 H, O-CH_3), 3.05 (m, 1 H, O-C-CH_2a-N), 2.91 (m, 1 H, O-C-CH_2b-N), 2.70 (ddd, J = 20.2 Hz, J = 13.5 Hz, J = 5.7 Hz, 2 H, N-CH_2a), 2.35-2.15 (m, 3 H, N-CH_2b & CH), 2.0-1.7 (m, 4 H, CH_2a's & CH_2b's), 1.25 (t, J = 7.2 Hz, 3 H, CH_3); ^13H NMR (75.5 MHz, $CDCl_3$) 175.0, 162.3, 135.7, 135.5, 133.4, 126.6, 118.9, 117.1, 105.2, 104.3, 71.9, 66.8, 60.2, 58.5, 54.1, 53.1, 51.8, 40.8, 28.3, 28.2, 14.1; HRMS, m/e 402.1802 ($C_21H_26N_2O_6$ requires 402.1791); Anal. Calcd for $C_21H_26N_2O_6$: C, 62.68; H, 6.51; N, 6.96. Found: C, 62.61; H, 6.70; N, 6.88. For the hydrochloride salt: Anal. Calcd for $C_21H_26N_2O_6$ HCl: C, 57.47; H, 6.20; N, 6.38. Found: C, 57.14; H, 6.27; N, 6.47.

Example 9: Preparation of 7H-1,4-Dioxino(2,3-e)indole-8-carboxylic acid, 2-((4-(aminocarbonyl)-4-(phenylamino)-1-piperidinyl)methyl)-2,3-dihydro-, methyl ester, **XIi**

A solution of **X** (125 mg, 0.300 mmol), 4-anilino-4-carbamylpiperidine (132 mg, 0.600 mmol), and powdered, anhydrous potassium carbonate (207 mg, 1.50 mmol) in dry pyridine (3 mL) was stirred overnight under nitrogen at 75°C. After cooling to room temperature, the black mixture was diluted with dichloromethane and filtered through non-absorbent cotton. The filtrate was concentrated in vacuo, allowing a small amount of pyridine to remain. The residue was chromatographed on 8 g of 230-400 mesh silica gel using 5% methanol/ethyl acetate to give 80 mg (58%) of **XIi** as a yellow-brown solid due to bleeding of an unknown dark substance on the column. The material was recrystallized from methanol/ethyl acetate to give a flocculent, off-white solid, mp 240-241°C (dec): R_f 0.14 (5% methanol/ethyl acetate); IR (mull) 3314, 2954, 2927, 2855, 1685, 1655, 1529, 1449, 1264, 1246 cm^{-1}; 1H NMR (300 MHz, DMSO-d6) 11.85 (broad s, 1 H, indole N-H), 7.22 (broad s, 1 H, NH_2a), 7.10 (broad s, 1 H, NH_2b), 7.06 (m, 2 H, meta Ph H's), 6.98 (s, 1 H, vinylic H), 6.92 (d, J = 8.8 Hz, 1 H, aromatic H), 6.87 (d, J = 8.7 Hz, 1 H, aromatic H), 6.59 (m, 3 H, ortho & para Ph H's), 4.43 (m, 1 H, O-CH), 4.29 (broad d, J = 10.8 Hz, 1 H, O-CH_2a), 3.99 (m, 1 H, O-CH_2b), 3.85 (s, 3 H, O-CH_3), 2.85-2.3 (m, 6 H, N-CH_2's), 2.1-1.8 (m, 4 H, CH_2a's & $CH2_b$'s); 13C NMR (75.5 MHz, DMSO-d6) 179.5, 163.3, 147.3, 136.8,

135.7, 130.3, 128.4, 120.0, 118.5, 118.3, 116.5, 106.9, 105.5, 73.5, 68.1, 59.6, 58.6, 53.5, 51.3, 50.6, 33.4, 33.0; HRMS, m/e 464.2058 ($C_25H_28N_4O_5$ requires 464.2060); Anal. Calcd for $C_25H_28N_4O_5$: C, 64.64; H, 6.08; N, 12.06. Found: C, 64.47; H, 6.26; N, 12.13.

Example 10: Preparation of 7H-1,4-Dioxino(2,3-e)indole-8-carboxylic acid, 2,3-dihydro-2-((3-phenylpropyl)amino)methyl)-, methyl ester, monohydrochloride, **XIj**

A solution of **X** (162 mg, 0.388 mmol) and potassium carbonate (107 mg, 0.776 mmol) in 3-phenyl-1-propylamine (1.0 mL) was stirred under nitrogen at 75°C for 5 h. A thick gel developed during this time. After cooling to room temperature, the mixture was taken-up in water (25 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (5 mL) and dried over anhydrous sodium sulfate. After concentration in vacuo to remove the dichloromethane, the excess of amine was ditilled-off (Kugelrohr) at 80°C and 0.1 mmHg. The residue was chromatographed on 20 g of 230-400 mesh silica gel using 40-75% ethyl acetate/hexane to give 70 mg (47%) of **XIj** as a colorless syrup which solidified to a white solid : R_f 0.23 (15% acetone/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 9.31 (broad s, 1 H, indole N-H), 7.22 (m, 6 H, phenyl H's & vinylic H), 6.92 (d, J = 8.8 Hz, 1 H, aromatic H), 6.88 (d, J = 8.8 Hz, 1 H, aromatic H), 4.42 (m, 1 H, O-CH), 4.30 (dd, J = 11.4 Hz, J = 2.2 Hz, 1 H, O-CH_2a), 4.06 (dd, J = 11.4 Hz, J = 7.0 Hz, 1 H, O-CH_2b), 3.92 (s, 3 H, O-CH_3), 2.99 (dd, J = 12.6 Hz, J = 7.0 Hz, 1 H, N-CH_2a-C-O), 2.90 (dd, J = 12.6 Hz, J = 4.6 Hz, 1 H, N-CH_2b-C-O), 2.69 (m, 4 H, N-CH_2 & Ph-CH_2), 1.85 (quint, J = 7.6 Hz, 2 H, CH_2), 1.63 (broad s, 1 H, N-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 162.3, 141.9, 135.7, 135.6, 133.4, 128.3, 128.2, 126.7, 125.7, 118.9, 117.2, 105.2, 104.4, 73.0, 66.4, 51.8, 49.8, 49.3, 33.4, 31.5.

Example 11: Preparation of 7H-1,4-Dioxino(2,3-e)indole-8-carboxamide, 2,3-dihydro-N-(3-phenylpropyl)-2-(((3-phenylpropyl)amino)methyl)-, monohydrochloride, **XIk**

A solution of **X** (162 mg, 0.388 mmol) and potassium carbonate (107 mg, 0.776 mmol) in 3-phenyl-1-propylamine (1.0 mL) was stirred under nitrogen at 75°C for 5 h. A thick gel developed during this time. After cooling to room temperature, the mixture was taken-up in water (25 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (5 mL) and dried over anhydrous

sodium sulfate. After concentration in vacuo to remove the dichloromethane, the excess of amine was ditilled-off (Kugelrohr) at 80°C and 0.1 mmHg. The residue was chromatographed on 20 g of 230-400 mesh silica gel using 40-75% ethyl acetate/hexane to give 82 mg (44%) of **XIk** as a white, waxy solid: 0.14 (15% acetone/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 10.10 (broad s, 1 H, indole N-H), 7.4-7.1 (m, 10 H, Ph H's), 6.89 (d, J = 8.8 Hz, 1 H, aromatic H), 6.85 (d, J = 8.8 Hz, 1 H, aromatic H), 6.75 (d, J = 1.7 Hz, 1 H, vinylic H), 6.24 (broad t, J = 5.8 Hz, 1 H, O=CN-H), 4.39 (m, 1 H, O-CH), 4.29 (dd, J = 11.4 Hz, J = 2.1 Hz, 1 H, O-CH_2a), 4.05 (dd, J = 11.4 Hz, J = 7.0 Hz, 1 H, O-CH_2b), 3.51 (quart, J = 6.7 Hz, 2 H, O=CN-CH_2), 2.98 (dd, J = 12.6 Hz, J = 7.1 Hz, 1 H, O-C-CH_2a-N), 2.88 (dd, J = 12.6 Hz, J = 4.7 Hz,1 H, O-C-CH_2b-N), 2.71 (m, 6 H, N-CH_2 & Ph-CH_2's), 1.95 (quint, J = 7.3 Hz, 2 H, O=CN-C-CH_2), 1.84 (quint, J = 7.6 Hz, 2 H, CH_2); ^{1}3C NMR (75.5 MHz, $CDCl_3$) 161.6, 141.9, 141.2, 135.5, 135.2, 133.0, 130.4, 128.5, 128.3, 126.0, 125.7, 118.8, 115.9, 104.7, 98.2, 73.0, 66.5, 49.9, 49.4, 39.3, 33.4, 33.3, 31.6, 31.1.

Example 12: Preparation of 1,3,8-Triazaspiro(4.5)decan-4-one, 8-((2,3-dihydro-7H-1,4-dioxino(2,3-e)indol-2-yl)methyl)-1-phenyl, **XIm**

Preparation of XIm is structurally represented in Chart IV.

Step 1

A solution of lithium hydroxide monohydrate (190 mg, 4.52 mmol) in water (7 mL) was added to a solution of **IX** (595 mg, 2.26 mmol) in methanol (14 mL) under nitrogen and the solution was heated at 60°C for 1 hour. The methanol was removed in vacuo and additional water (20 mL) was added to the aqueous remainder. The pH was adjusted to 2 with 1 N hydrochloric acid and the resulting thick, white precipitate was filtered and washed well with water. After air-drying for some time, further drying in vacuo gave 540 mg (96%) of **XII** as a white powder. Recrystallization from ethyl acetate/ethanol/hexane (ethanol was added to a suspension of **XII** in ethyl acetate until a clear solution was obtained, followed by the addition of 1 vol. of hexane and subsequent cooling) gave an amorphous white solid.

Step 2

A round-bottom flask containing solid **XII** (407 mg, 1.63 mmol) under nitrogen was lowered into an oil bath preheated at 240°C. The temperature was raised to 257°C and maintained there for 30 min, during which time gas evolution occurred. After cooling to room temperature, the resulting resin was dissolved in

ethyl acetate, and the solution concentrated in vacuo. The residue was taken up in 75% ethyl acetate/hexane and chromatographed on 40 g of 230-400 mesh silica gel using 40% ethyl acetate/hexane to give 208 mg (62%) of **XIII** as a near colorless syrup: R_f 0.23 (40% ethyl acetate/hexane).

Step 3

p-Toluenesulfonyl chloride (212 mg, 1.11 mmol) was added in a single portion to a solution of **XIII** (190 mg, 0.926 mmol) and 4-dimethylaminopyridine (147 mg, 1.20 mmol) in dry dichloromethane (9 mL) at 0°C under nitrogen. The cooling bath was removed and the solution was stirred at room temperature for 23 hours. The mixture was transferred to a separatory funnel with additional dichloromethane (15 mL) and washed with water (1 x 5 mL), saturated aqueous copper sulfate (2 x 5 mL), and water (1 x 5 mL), then dried over anhydrous sodium sulfate. After filtration and concentration in vacuo, the resulting greenish solid was adsorbed onto 1 g of 230-400 mesh silica gel (from ethyl acetate) and chromatographed on 20 g of 230-400 mesh silica gel using 25-30% ethyl acetate/hexane. The syrup initially obtained was dissolved in 60% ethyl acetate/hexane (several mL's) where 200 mg of **XIV** was deposited as a white, crystalline solid, mp 145-145.5°C; the essentially pure mother liquor amounted to 90 mg (total yield 87%): R_f 0.32 (40% ethyl acetate/hexane).

Step 4

A solution of **XIV** (237 mg, 0.659 mmol), 1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one (458 mg, 1.98 mmol), and powdered, anhydrous potassium carbonate (456 mg, 3.30 mmol) in dry pyridine (7 mL) was heated at 75°C under nitrogen overnight. The black mixture was diluted with dichloromethane (1 vol) and filtered through Celite, washing the black sludge well with dichloromethane. The filtrate was concentrated in vacuo (a slight amount of pyridine was allowed to remain), and the residue was taken-up in a large volume of dichloromethane and chromatographed on 20 g of 230-400 silica gel using 75% ethyl acetate/hexane to give 152 mg (55%) of **XIm** as a yellowed solid; for analysis, recrystallization from ethyl acetate/ethanol/hexane gave a pale yellow-tan solid, mp 228-230 (dec): R_f 0.17 (75% ethyl acetate/hexane); 2955, 2925, 2854, 1711, 1511, 1497, 1456, 1360, 1236, 1094 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) 10.93 (broad s, 1 H, indole N-H), 8.65 (broad s, 1 H, lactam N-H), 7.25 (t, J = 7.7 Hz, 2 H, phenyl meta H's), 7.19 (t, J = 2.7 Hz, 1 H, vinylic H), 6.86 (m, 3 H, phenyl ortho H's & aromatic H), 6.76 (t,

J = 7.3 Hz, 1 H, phenyl para H), 6.65 (d, J = 8.6 Hz, 1 H, aromatic H), 6.31 (m, 1 H, vinylic H), 4.58 (s, 2 H, N-CH_2-N), 4.43 (m, 1 H, O-CH), 4.34 (m, 1 H, O-CH_2a), 4.02 (dd, J = 11.3 Hz, J = 6.7 Hz, 1 H, O-CH_2b), 3.0-2.5 (m, 8 H, N-CH_2's & N-C-CH_2a's), 1.57 (m, 2 H, N-C-CH_2b's); ^{13}C NMR (75.5 MHz, DMSO-d6) 176.2, 143.3, 134.6, 134.4, 132.3, 129.0, 124.6, 118.4, 117.6, 114.2, 112.0, 104.0, 97.4, 71.4, 66.3, 58.7, 58.0, 57.8, 50.7, 49.6, 28.5; HRMS, m/e 418.2015 ($C_24H_26N_4O_3$ requires 418.2005); Anal. Calcd for $C_24H_26N_4O_3$: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.60; H, 6.19; N, 13.39.

The following compounds can also be synthesized using variations on the Examples described above:

7H-1,4-Dioxino(2,3-e)indole-8-carboxylic acid 2,3,8,9-tetrahydro-2-((4-oxo-1-phenyl-1,3,8-triazaspiro(4.5)dec-8-yl)methyl)-, methyl ester, **XIa'**;

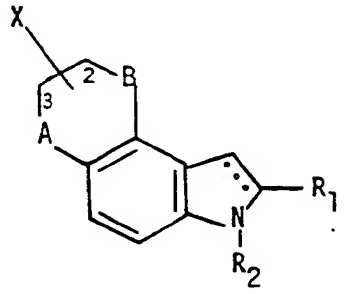
1,3,8-Triazaspiro(4.5)decan-4-one, 8-((2,3-dihydro-8-(hydroxymethyl)-7H-1,4-dioxino(2,3-e)indol-2-yl)methyl)-1-phenyl-, **XII**;

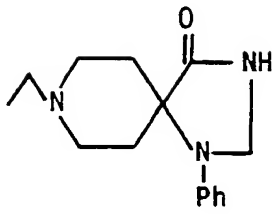
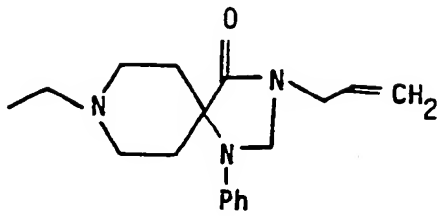
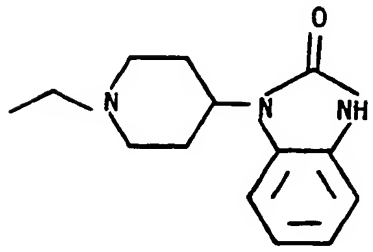
7H-1,4-Dioxino(2,3-e)indole-8-carboxylic acid, 2,3-dihydro-2-((4-oxo-1-phenyl-1,3,8-triazaspiro(4.5)dec-8-yl)methyl)-7-(2-propenyl)-, methyl ester, **XIn**;

7H-1,4-Dioxino(2,3-e)indole-8-carboxylic acid, 2,3-dihydro-2-((4-oxo-1-phenyl-3-(2-propenyl)-1,3,8-triazaspiro(4.5)dec-8-yl)methyl)-7-(2-propenyl)-, methyl ester, **XIo**; and

7H-1,4-Dioxino(2,3-e)indole-8-carboxylic acid, 2,3-dihydro-2-((4-oxo-1-phenyl-3-(2-propenyl)-1,3,8-triazaspiro(4.5)dec-8-yl)methyl)-, methyl ester, **XIp**.

Formula I Structures



Compound	X	R_1	R_2	A	B
XI a (2)		$-CO_2CH_3$	H	0	0
a' (2)	"	$-CO_2CH_3$ (racemate)			
a" (3)	"	$-CO_2CH_3$	H	0	0
b (2)	"	$-CO_2CH_3$	H	0	0
c	"	$-CO_2H$	H	0	0
d	"	-CN	H	0	0
e	"	$-CO_2C_4H_9$	H	0	0
f	"	$-CO_2CH_2$-Ph	H	0	0
l	"	$-CH_2OH$	H	0	0
m	"	H	H	0	0
n	"	$-CO_2CH_3$	$-CH_2-CH=CH_2$	0	0
o (2)		"	"	0	0
p	"	"	H	0	0
g (2)		"	H	0	0

Formula I Structures - continued

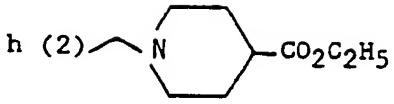
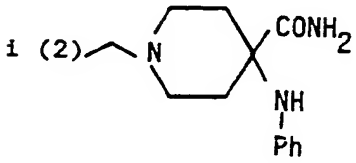
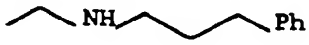
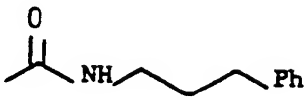
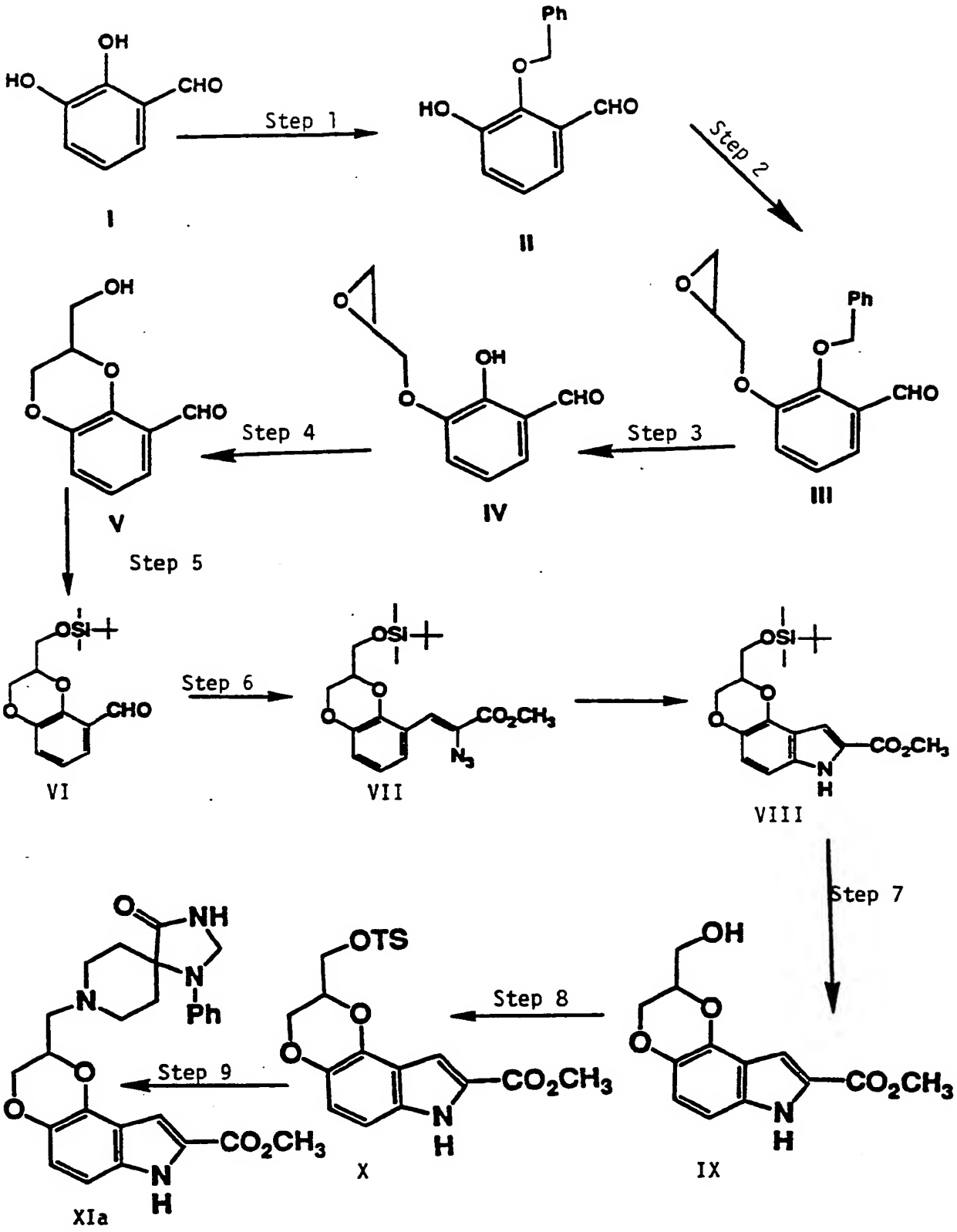
Compound	X	R_1	R_2	A	B
h	(2) 	"	H	0	0
i	(2) 	"	H	0	0
j	(2) 	"	H	0	0
k	" 		H	0	0

CHART I


OH
HO
CHO
I
Step 1
Ph
O
HO
CHO
II
Step 2
O
Ph
O
O
CHO
III
Step 3
O
OH
O
CHO
IV
Step 4
OH
O
O
CHO
V
Step 5
OSi
O
O
CHO
VI
Step 6
OSi
O
O
CO2CH3
N3
VII
OSi
O
O
CO2CH3
N
H
VIII
Step 7
OH
O
O
CO2CH3
N
H
IX
Step 8
OTS
O
O
CO2CH3
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H
X
Step 9
O
NH
N
Ph
N
O
O
CO2CH3
N
H
XIa

CHART II

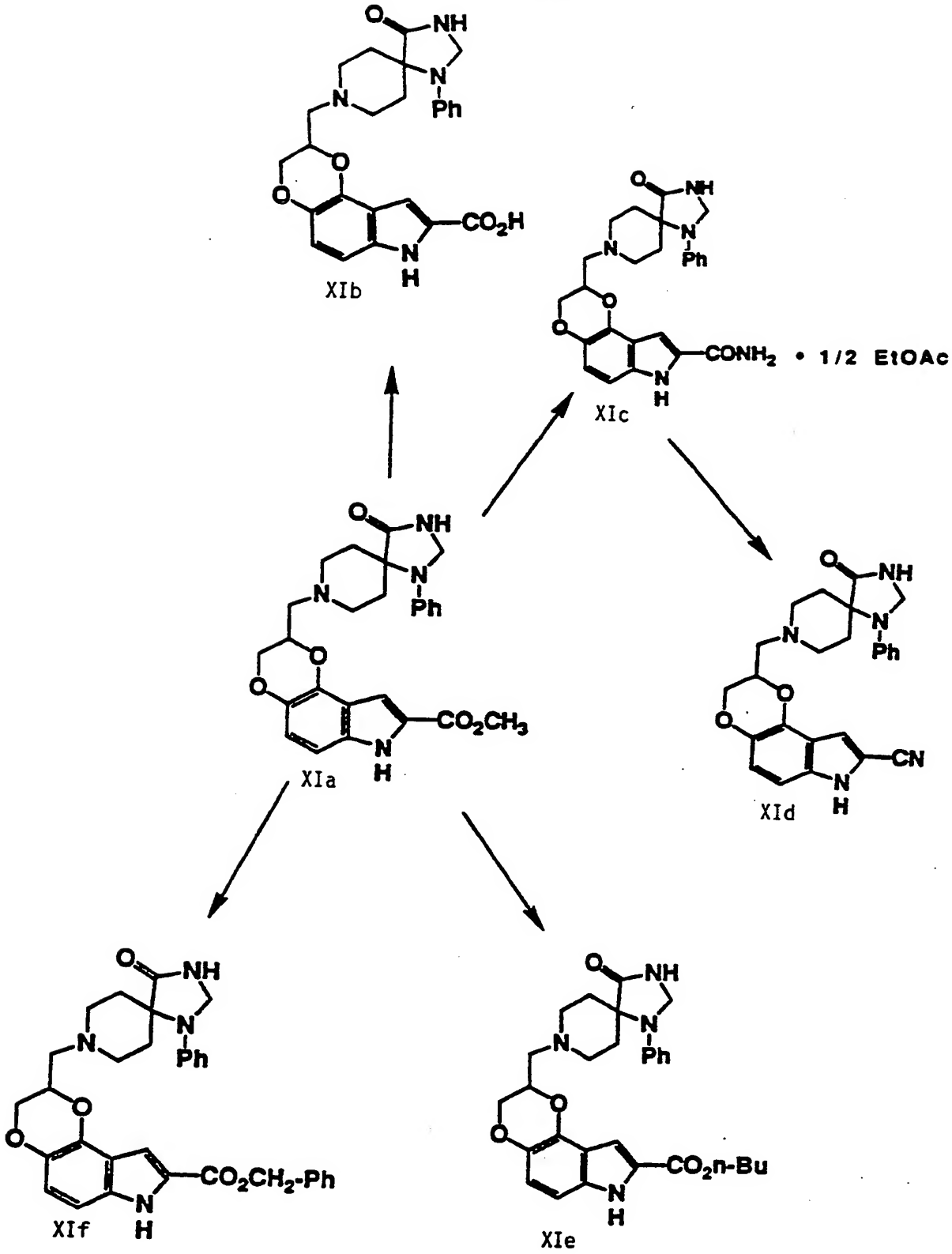


CHART III

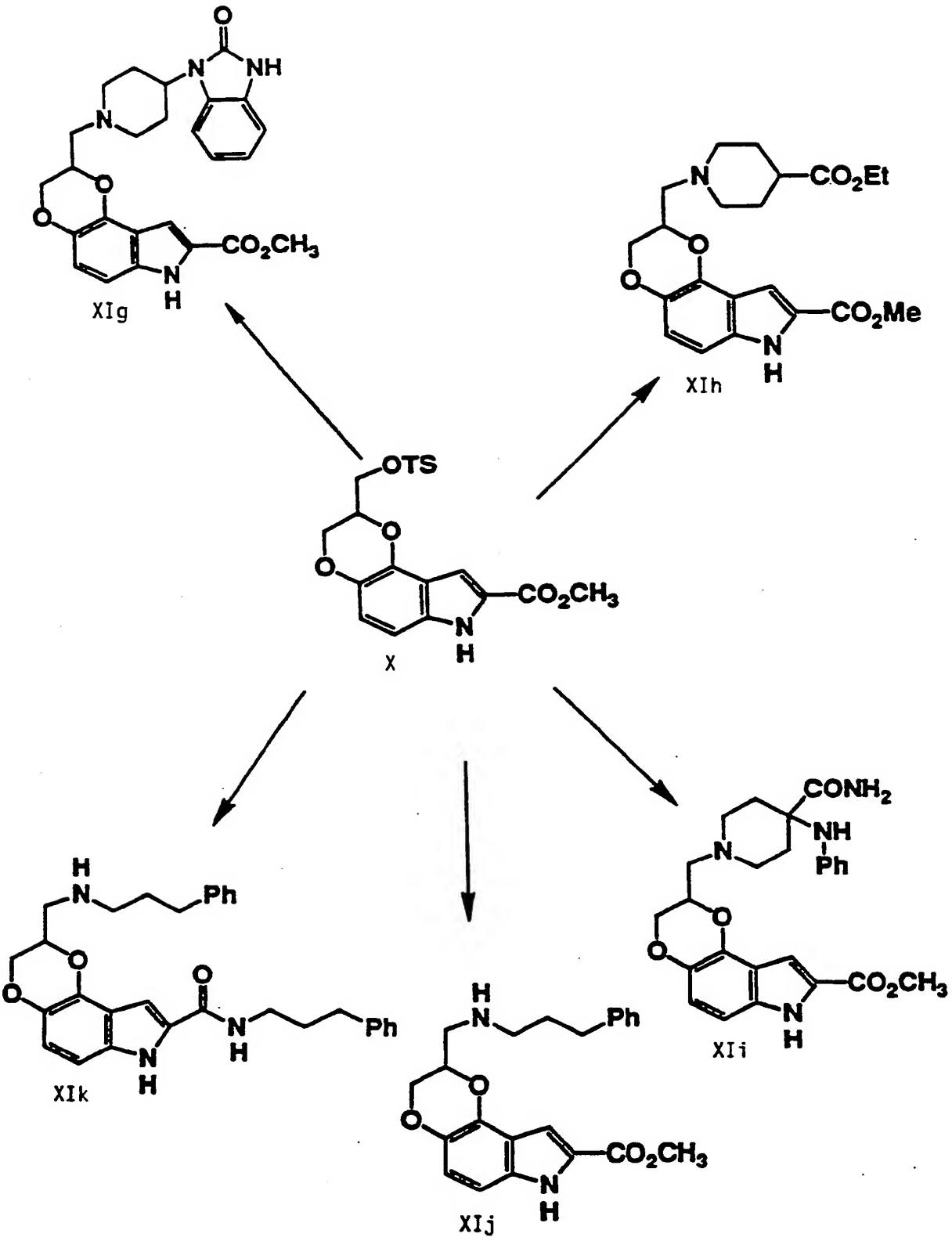
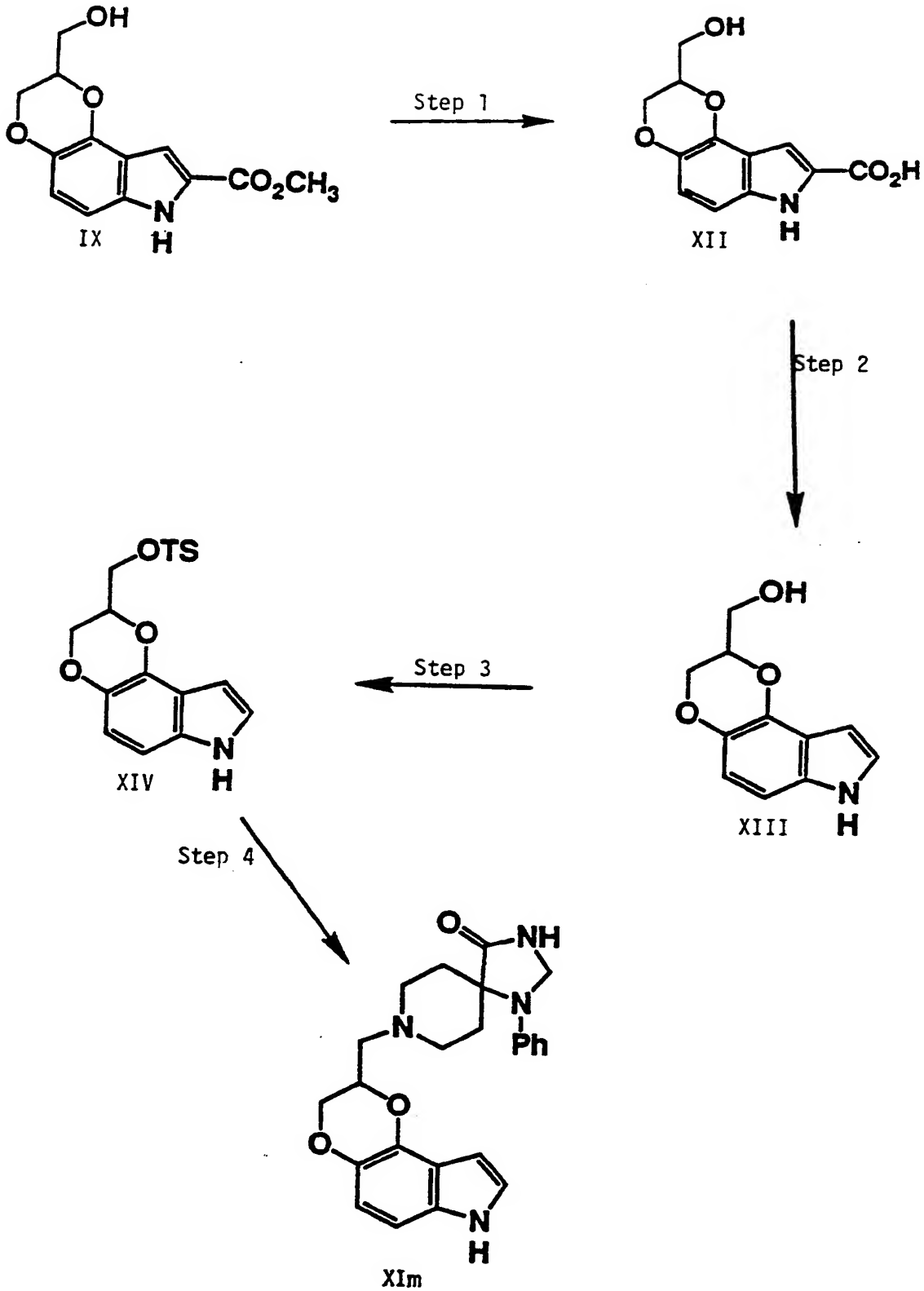
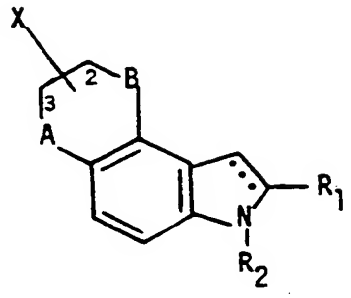


CHART IV



CLAIMS

1. A compound having the structural formula:



I

or pharmaceutically acceptable salts thereof wherein;

R_1 is hydrogen,

C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl,

$-CO_2R_2$,

$-CONHR_2$,

-CN,

halogen,

-CHO,

$-(CH_2)_m-OR_2$,

$-(CH_2)_m$-Ar, or

$-SO_2R_2$;

R_2 is hydrogen,

C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl,

$-(CH_2)_m(C_3-C_8)$ cycloalkyl or cycloalkenyl, or

$-(CH_2)_m$-Ar where Ar is phenyl, pyridyl, naphthyl, indolyl optionally substituted with $-OR_2$, halogen, -CN, -CHO,

$-(CH_2)_m$-Ph, $-NO_2$, $-SR_2$ or NHR_2 and m is 0 to 6;

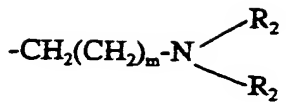
A and B are independently

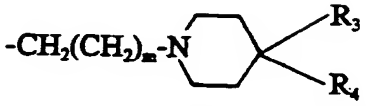
oxygen,

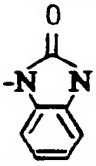
CH_2 or

sulfur; and

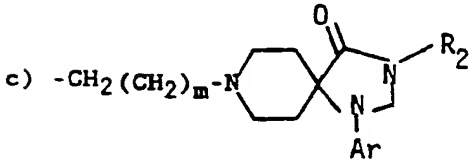
X is

a) 

b) 

where R_3 is hydrogen, $-CO_2R_2$, $-CONHR_2$, $-CN$, $-NHR_2$, $-CHO$, $-(CH_2)_m-Ar$, $-NR_2Ar$ or  and

R_4 is hydrogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(CH_2)_m-(C_3-C_8)$ cycloalkyl or cycloalkenyl, $-(CH_2)_m-Ar$, $-CO_2R_2$, $-CONHR_2$, $-CN$ or $-CHO$; or

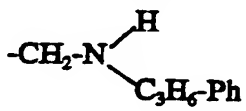
c) 

2. The compound of Claim 1 wherein A and B are 0.

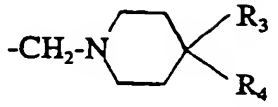
3. The compound of Claim 1 wherein R_2 is hydrogen.

4. The compound of Claim 2 wherein R_1 is $-CO_2R_2$.

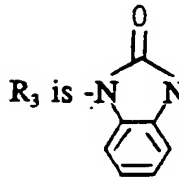
5. The compound of Claim 1 wherein X is



6. The compound of Claim 1 wherein X is

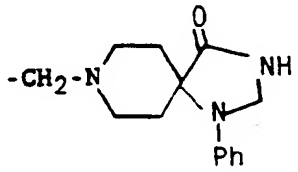


where

R_3 is  , -NHPh, or $-CO_2C_2H_5$ and

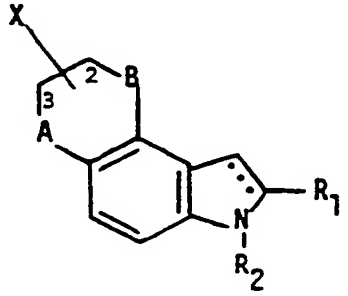
R_4 is hydrogen or $-CONH_2$.

7. The compound of Claim 2 wherein X is



8. A use of a compound of Formula I for the manufacture of a medicament for treating central nervous system and cardiovascular system disorders related to $5HT_{1A}$ neuronal activity or dopamine receptor activity comprising:

administering a therapeutically effective amount of a compound of Formula I



I

or pharmaceutically acceptable salts thereof wherein;

R_1 is hydrogen,

C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl,

$-CO_2R_2$,

$-CONHR_2$,

-CN,

halogen,

-CHO,

$-(CH_2)_m-OR_2$,

$-(CH_2)_m$-Ar, or

$-SO_2R_2$;

R_2 is hydrogen,

C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl,

$-(CH_2)_m(C_3-C_8)$ cycloalkyl or cycloalkenyl, or

$-(CH_2)_m$-Ar where Ar is phenyl, pyridyl, naphthyl, indolyl optionally substituted with $-OR_2$, halogen, -CN, -CHO, $-(CH_2)_m$-Ph, $-NO_2$, $-SR_2$ or NHR_2 and m is 0 to 6;

A and B are independently

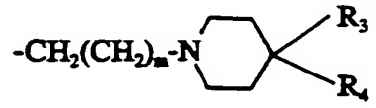
oxygen,

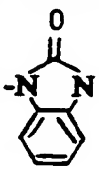
CH_2 or

sulfur; and

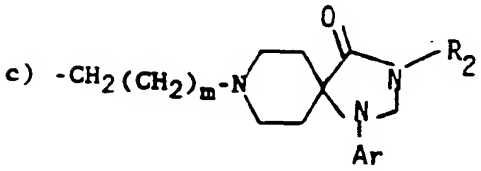
X is

a) $-CH_2(CH_2)_m-N(R_2)(R_2)$

b) 

where R_3 is hydrogen, $-CO_2R_2$, $-CONHR_2$, -CN, $-NHR_2$, -CHO, $-(CH_2)_m$-Ar, $-NR_2Ar$ or  and

R_4 is hydrogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(CH_2)_m$-(C_3-C_8) cycloalkyl or cycloalkenyl, $-(CH_2)_m$-Ar, $-CO_2R_2$, $-CONHR_2$, -CN or -CHO; or

c) 

9. The method of Claim 8 where said compound of Formula I is administered in an amount of from about 1-2000 mg orally or from about 0.1 to 100 mg parenterally.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/00117

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 209/60, 491/052, 491/056, 495/04, 497/04, 519/00, A 61 K 31/40, 31/445,//(C 07 D 491/056, 319:00, 209:00), ./.

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D, A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0055043 (AYERST, McKENNA & HARRISON INC.) 30 June 1982 see claim 1; page 2, lines 1-11 --	1,8
A	EP, A, 0109039 (YOSHITOMI) 23 May 1984 see claim 1; page 5, lines 16-22 cited in the application --	1,8
A	Chemical Abstracts, vol. 106, no. 23, 8 June 1987, (Columbus, Ohio, US), D.A. Partsvaniya et al.: "Synthesis and pharmacological activity of 5,6- and 4,5-ethylendioxytryptamines", see pages 737-738, abstract 196345r, & Khim.-Farm. Zh. 1986, 20(12), 1454-9 cited in the application ----------	1,8

* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22nd May 1991	25 JUN 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Danielle van der Haas

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/00117

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: (C 07 D 519/00, 491:00, 471:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]

[10] Special categories of cited documents:

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Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
	25 JUN 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Danielle van der Haas

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9100117 SA 44886

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0055043	30-06-82	US-A- 4370341	25-01-83
		US-A- 4454150	12-06-84
		AT-T- E11406	15-02-85
		CA-A- 1159459	27-12-83
		JP-A- 57126472	06-08-82
EP-A- 0109039	23-05-84	WO-A- 8401948	24-05-84

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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C07D 239:00, 221:00)
(C07D 513/04, 277:00, 239:00)

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Filed on 13 July 1992 (13.07.92)

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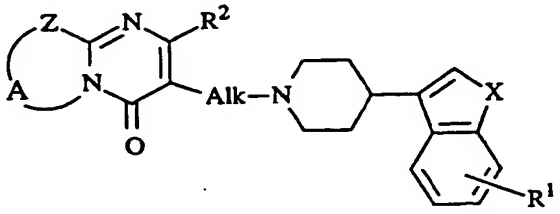
Published
With international search report.

(54) Title: NOVEL 4-(3-BENZOFURANYL)PIPERIDINYL AND 4-(3-BENZOTHIENYL)PIPERIDINYL DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(I)

(57) Abstract

The invention is concerned with novel compounds of formula (I), the pharmaceutically acceptable acid addition salts thereof and the stereochemically isomeric forms thereof, wherein X is oxygen or sulphur; R^1 is hydrogen or halo; R^2 is hydrogen, C_{1-4}alkyl, phenylmethyl or halophenylmethyl; Alk is C_{1-4}alkanediyl; -Z-A- is a bivalent radical selected from the group consisting of -S-CH_2-CH_2, -S-CH_2-CH_2-CH_2-, -S-CH=CH-, -CH=CH-CH=CH-, -C(=CHR^3)-CH_2-CH_2-CH_2-, -CH=CH-O-, -CHR^4-CH_2-CH_2-, -CHR^4-CH_2-CH_2-CH_2-, -CHR^4-CH_2-CH_2-CH_2-CH_2-; in said bivalent radicals one hydrogen may be replaced by C_{1-4}alkyl; R^3 is phenyl or halophenyl; each R^4 independently represents hydrogen, hydroxy, phenylmethyl or halophenylmethyl. Pharmaceutical compositions of said compounds and use as a medicine.

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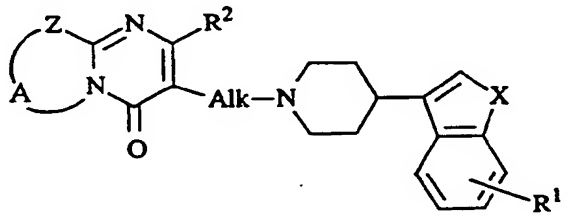
NOVEL 4-(3-BENZOFURANYL)PIPERIDINYL AND 4-(3-BENZOTHIENYL)PIPERIDINYL DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Background of the invention

In US 4,804,663 there are described 1,2-benzisoxazol-3-yl and 1,2-benzisothiazol-3-yl derivatives having antipsychotic and antiserotonin activity. In EP-A-0,378,255 there are described 4-aminopyrimidinone derivatives as antagonists of the neurotransmitters serotonin and histamine. In JP-A-2-63911 there are described benzothiophene- and benzofuranderivatives as 5-HT_2 receptor antagonists useful for treating ischaemic heart disease, cerebrovascular disease, depression or schizophrenia. The present compounds differ structurally and show a different pharmacological profile.

Description of the invention

The invention is concerned with novel compounds of the formula



(I),

the pharmaceutically acceptable acid addition salts thereof and the stereochemically isomeric forms thereof, wherein

X is oxygen or sulphur;

R^1 is hydrogen or halo;

R^2 is hydrogen, C_{1-4}alkyl, phenylmethyl or halophenylmethyl;

Alk is C_{1-4}alkanediyl;

-Z-A- is a bivalent radical selected from the group consisting of -S-CH_2-CH_2-, -S-CH_2-CH_2-CH_2-, -S-CH=CH-, -CH=CH-CH=CH-, -C(=CHR^3)-CH_2-CH_2-CH_2-, -CH=CH-O-, -CHR^4-CH_2-CH_2-, -CHR^4-CH_2-CH_2-CH_2-, -CHR^4-CH_2-CH_2-CH_2-CH_2-; wherein in said bivalent radicals one hydrogen may be replaced by C_{1-4}alkyl;

R^3 is phenyl or halophenyl; and

each R^4 independently represents hydrogen, hydroxy, phenylmethyl or halophenylmethyl.

In the foregoing and hereinafter C_{1-4}alkanediyl defines bivalent straight and branched chain alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the branched isomers thereof; halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branch chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1,1-dimethylethyl, 1-methyl-propyl, 2-methylpropyl and the like; and halophenylmethyl defines fluorophenylmethyl, chlorophenylmethyl, bromophenylmethyl, iodophenylmethyl and the like.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have either the R- or the S-configuration; substituents on bivalent cyclic saturated hydrocarbon radicals may have either the cis- or trans-configuration and radicals or moieties containing double bonds may have the E- or Z-configuration. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with appropriate acids such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic acid and the like, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids such as, for example, acetic, hydroxyacetic, propanoic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form. The term acid addition salt also comprises the hydrates and solvent addition forms which the

compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

R^1 is suitably hydrogen or fluoro;
R^2 is suitably phenylmethyl or C_{1-4}alkyl, preferably methyl;
Alk is suitably C_{2-3}alkanediyl, preferably 1,2-ethanediyl or 1,3-propanediyl;
R^3 is suitably phenyl or fluorophenyl, especially 4-fluorophenyl;
R^4 is suitably hydrogen, hydroxy or halophenylmethyl, especially fluorophenylmethyl.

Particular compounds are those compounds of formula (I), wherein -Z-A- is a bivalent radical of formula -S-CH_2-CH_2-, -S-CH_2-CH_2-CH_2-, -S-CH=CH-, -S-CH=C(CH_3)-, -CH=CH-CH=CH-, -C(CH_3)=CH-CH=CH-, -CH=CH-O-, or -CH=C(CH_3)-O-.

Also particular compounds are those compounds of formula (I), wherein -Z-A- is a bivalent radical of formula -CHR^4-CH_2-CH_2-, -CHR^4-CH_2-CH_2-CH_2-, or -CHR^4-CH_2-CH_2-CH_2-CH_2-, wherein R^4 is hydrogen, hydroxy or halophenylmethyl, especially fluorophenylmethyl; or -C(=CHR^3)-CH_2-CH_2-CH_2-, wherein R^3 is phenyl or halophenyl, particularly 4-halophenyl, especially fluorophenyl, preferably 4-fluorophenyl.

A first group of particularly interesting compounds are those compounds, wherein Alk is 1,2-ethanediyl or 1,3-propanediyl, R^4 is hydrogen and X is oxygen or sulfur, preferably oxygen.

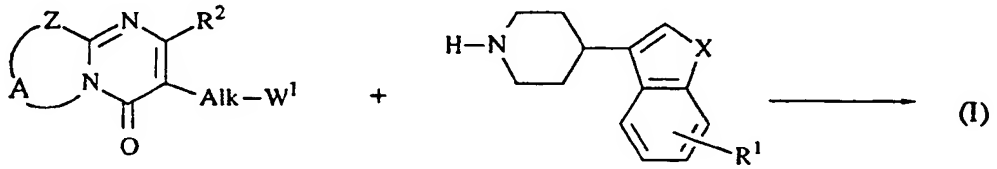
Another group of particularly interesting compounds are those compounds, wherein -Z-A- is a bivalent radical of formula -S-CH_2-CH_2-, -S-CH_2-CH_2-CH_2-, -S-CH=CH-, -CH=CH-CH=CH-, -CH_2-CH_2-CH_2-CH_2-, or -CH=C(CH_3)-O-.

Preferred compounds are :
6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2,3-dihydro-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one ;
3-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one ;
6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo-[3,2-a]pyrimidin-5-one ;
6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2,5-dimethyl-7H-isoxazolo-[2,3-a]pyrimidin-7-one ;

6-[2-[4-(3-benzo[b]thienyl)-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one ;
3-[2-[4-(3-benzo[b]thienyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one
3-[2-[4-(3-benzo[b]thienyl)-1-piperidinyl]ethyl]-2,9-dimethyl-4H-pyrido-[1,2-a]pyrimidin-4-one ;
3-[3-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]propyl]-2,9-dimethyl-4H-pyrido-[1,2-a]pyrimidin-4-on4 ;
3-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2-(phenylmethyl)-4H-pyrido-[1,2-a]pyrimidin-4-one, the stereochemically isomeric forms and the pharmaceutically acceptable acid addition salts thereof.

Most preferred compounds are :
3-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one,
6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo-[3,2-a]pyrimidin-5-one
and the pharmaceutically acceptable acid-addition salts thereof.

The compounds of formula (I) can generally be prepared by N-alkylating an intermediate of formula (II) with an intermediate of formula (III). In formula (III) and the formulae hereinafter, W^1 represents a reactive leaving group such as, for example, halo, e.g. chloro, bromo or iodo, or a sulfonyloxygroup, e.g. methanesulfonyloxy, 4-methylbenzenesulphonyloxy and the like.

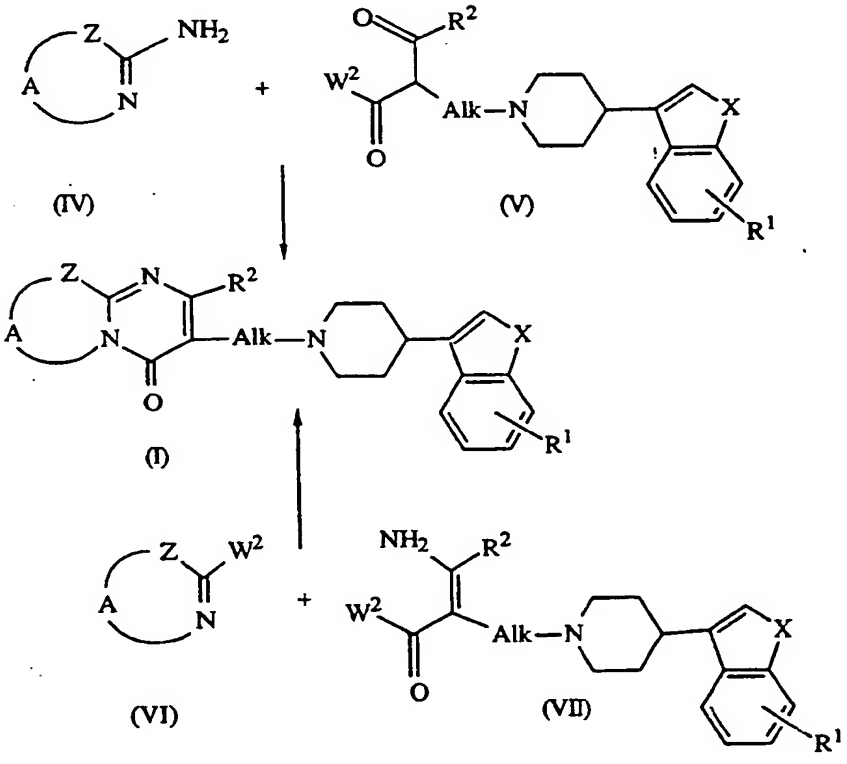


(III) (II)

The reaction of (II) with (III) can conveniently be conducted in a reaction-inert organic solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, methylbenzene, dimethylbenzene and the like; a lower alkanol, e.g. methanol, ethanol, 1-butanol and the like; a ketone, e.g. 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g. 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran and the like; N,N-dimethylformamide, N,N-dimethylacetamide, nitrobenzene, 1-methyl-2-pyrrolidinone and the like. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, hydroxide, alkoxide or hydride, e.g. sodium carbonate,

sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, sodium methoxide, sodium hydride and the like, or an organic base such as, for example, a tertiairy amine, e.g. N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine and the like, may be useful to pick up the acid which is liberated during the course of the reaction. In some circumstances the addition of a iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures may enhance the rate of the reaction.

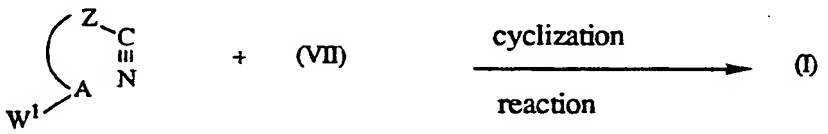
The compounds of formula (I), can also be prepared following art-known cyclizing procedures for preparing pyrimidin-4-ones such as, for example, by reacting an amine of formula (IV) with a β-dicarbonyl derivative of formula (V) or by cyclizing a reagent of formula (VI) with an enamine of formula (VII). In formula (V) and in the formulae hereinafter each W^2 independently represents an appropriate leaving group such as, for example, hydroxy, halo, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyloxy, amino, mono- or di(C_{1-4}alkyl)amino.



Said cyclization reactions may generally be carried out by stirring the reactants, optionally in the presence of a suitable reaction-inert solvent such as, for example, an aliphatic, alicyclic or aromatic hydrocarbon, e.g. hexane, cyclohexane or benzene and the like; or pyridine, N,N-dimethylformamide and the like dipolar aprotic solvents. Elevated

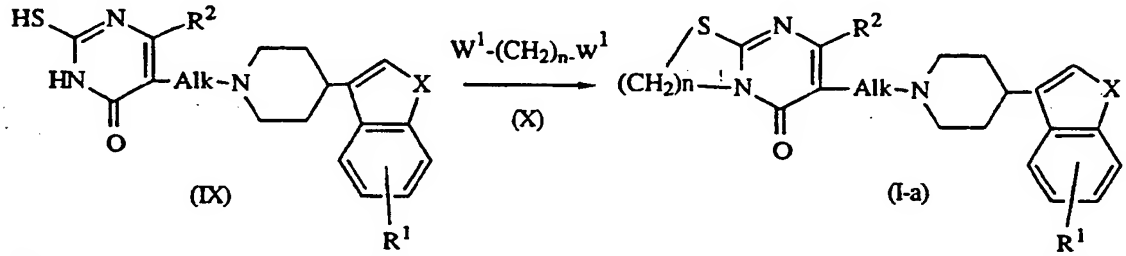
temperatures may be appropriate to enhance the reaction rate; more in particular it may be advantageous to carry out the reaction at the reflux temperature of the reaction mixture.

Following the same procedure the compounds of formula (I) can also be prepared by cyclizing an intermediate of formula (VII) with a reagent of formula (VIII).



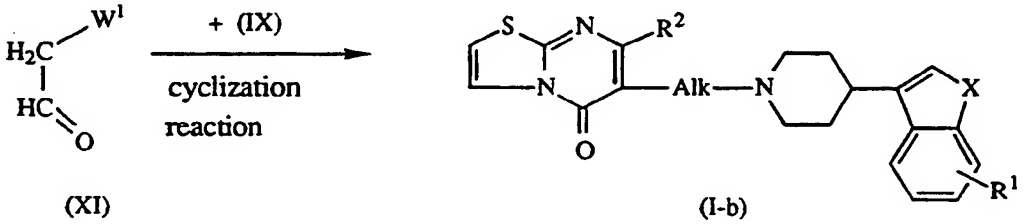
(VIII)

The compounds of formula (I) wherein Z-A is a bivalent radical -S-CH_2-CH_2- or -S-CH_2-CH_2-CH_2- and wherein in said bivalent radicals one hydrogen may be replaced by C_{1-4}alkyl, said compounds being represented by the formula (I-a), can also be prepared by cyclizing a 2-mercaptopyrimidinone of formula (IX) with a reagent of formula (X), wherein n is 2 or 3 and wherein one hydrogen may be replaced by C_{1-4}alkyl.



(IX) (I-a)

The compounds of formula (I) wherein Z-A is a bivalent radical of formula -S-CH=CH-, wherein one hydrogen may be replaced by C_{1-4}alkyl, said compounds being represented by the formula (I-b), can be prepared by cyclizing a 2-mercapto-pyrimidinone of formula (IX) with a reagent of formula (XI) wherein one hydrogen atom may be replaced by C_{1-4}alkyl.



(XI) (I-b)

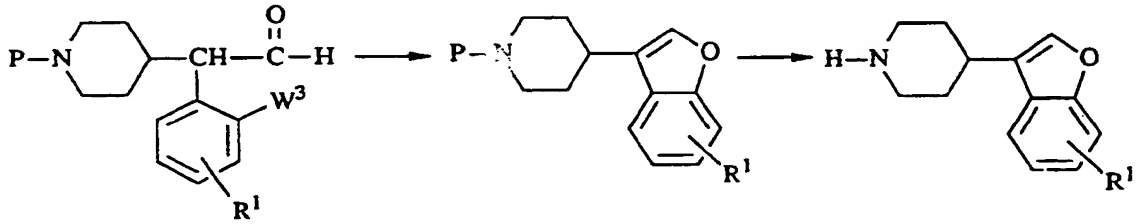
Said cyclization reactions for preparing the compounds of formulae (I-a) and (I-b) may generally be carried out by stirring the reactants, if desired, in the presence of a suitable reaction-inert solvent such as, for example, an aliphatic, alicyclic or aromatic hydro-

carbon, e.g. hexane, cyclohexane or benzene and the like; or pyridine, N,N-dimethylformamide and the like dipolar aprotic solvents. Elevated temperatures may be appropriate to enhance the reaction-rate, more in particular it may be preferred to carry out the reaction at the reflux temperature of the reaction mixture.

The compounds of formula (I) may also be converted into each other using art-known functional group transformations. For example, compounds of formula (I), wherein R^1 is hydrogen may be converted into compounds of formula (I) wherein R^1 is halo using art-known halogenation techniques.

A number of intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds. The intermediates of formula (III) and their preparations are described in U.S. Patent No. 4,804,663 and in the references cited therein.

The intermediates of formula (II) wherein X is oxygen, said intermediates being represented by formula (II-a), can be prepared by cyclizing an aldehyde of formula (XII) and deprotecting the intermediate of formula (XIII). In formula (XII) and the formulae hereinunder P represents a protective group such as for example C_{1-6}alkylcarbonyl and W^3 represent a reactive leaving group such as, for example, halo, e.g. fluoro, chloro, bromo, iodo.

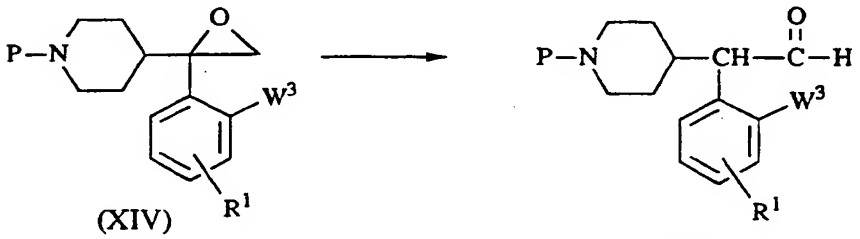


(XII) (XIII) (II-a)

Said cyclization may conveniently be conducted by treating the aldehyde of formula (XII) with an appropriate base in an reaction-inert organic solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, methylbenzene, dimethylbenzene and the like, an ether, e.g. 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran and like; a dipolar aprotic solvent, such as, for example N,N-dimethylformamide, N,N-dimethylacetamide and the like. Appropriate bases are for example alkali or earth alkaline metal carbonate, hydrogen carbonate, hydroxide, alkoxide, hydride, e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, sodium methoxide, sodium hydride and the like, or an organic base such as a tertiary amine, e.g.

N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine and the like.

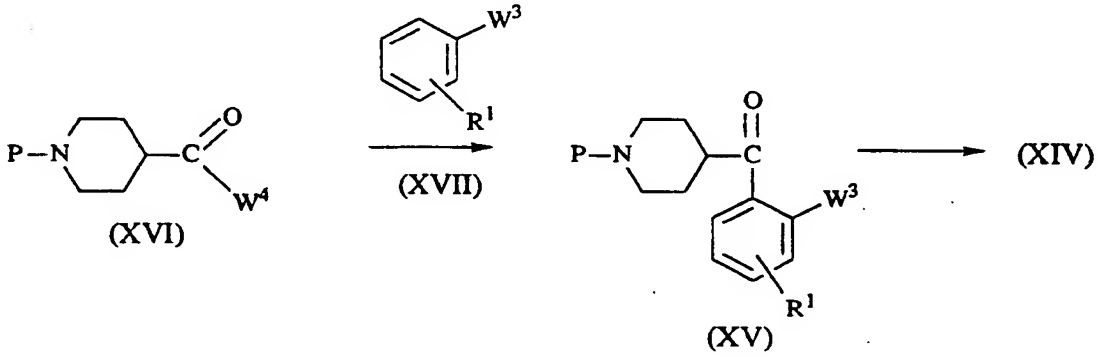
The intermediate aldehyde of formula (XII) can be prepared by reacting an epoxide of formula (XIV) with an acid, such as, for example, a mineral acid, e.g. perchloric acid, sulphuric acid and the like; a Lewis acid, e.g. borontrifluoride, magnesiumdibromide, aluminiumtrichloride and the like in an appropriate solvent.



(XIV) (XII)

Depending upon the nature of the acid, appropriate solvents are water; alkanols, e.g. methanol, ethanol and the like; aromatic hydrocarbons, e.g. benzene, methylbenzene, dimethylbenzene and the like; ethers, e.g. 1,1'oxybisethane, tetrahydrofuran and the like; halogenated hydrocarbons, e.g. dichloromethane, trichloromethane and the like. Stirring and elevated temperatures may enhance the rate of the reaction.

The epoxides of formula (XIV) can be obtained by stirring a ketone of formula (XV) with a sulphur ylide, such as dimethyloxosulfonium methylide or dimethylsulfonium methylide in an appropriate solvent, such as, for example, an ether, e.g. 1,1'-oxybis-ethane, tetrahydrofuran, 2,2'-oxybispropane and the like; a dipolar aprotic solvent, e.g. dimethylsulfoxide, N,N-dimethylacetamide, N,N-dimethylformamide and the like.



(XVI) (XVII) (XV) (XIV)

The ketones of formula (XV) can be prepared by a Friedel-Crafts acylation of piperidines of formula (XVI) wherein W^4 is a reactive leaving group such as for example hydroxy, halo, C_{1-4}carbonyloxy and the like, with benzenederivative of formula (XVII). Said

Friedel-Crafts acylation can be performed by stirring the reactants in the presence of an acid in a reaction-inert solvent, such as for example, an ether, e.g. 1,1'-oxybisethane, 2,2'-oxybispropane, tetrahydrofuran, dioxane and the like, a halogenated hydrocarbon, e.g. dichloromethane, trichloromethane and the like. Suitable acids are mineral acids such as sulphuric acid, phosphoric acid, phosphorous pentoxide and the like, Lewis acids, e.g. aluminiumtrichloride, ferric chloride, zinc chloride and the like.

The compounds of formula (I) and the pharmaceutically acceptable acid addition salts have useful pharmacological properties. For example, the compounds of formula (I) possess anti-dopamine activity and show good affinity for several serotonin receptors, especially $5HT_{1A}$. Said compounds can also inhibit neuronal serotonin reuptake. Furthermore the compounds of formula (I) antagonize the action of reserpine (cfr. Example 3). Due to their pharmacological activities, the compounds of formula (I) and their pharmaceutically acceptable acid addition salts can be used in the treatment of psychotic diseases and in the treatment of a variety of complaints in which serotonin is of predominant importance. The present compounds may block serotonin-induced contractions of bronchial tissues and of blood vessels, arteries as well as veins. Particularly in view of their reserpine-antagonizing activity the compounds of formula (I) also have useful properties as anti-depressants, anxiolytics, antitremor agents and show activity against obsessive compulsive disorders, such as anorexia, bulimia and addiction, e.g. alcohol abuse.

The compounds of the present invention therefore may be used as medicines against above-mentioned conditions. Said use as a medicine or method of treatment comprises the systemic administration to patients of an amount effective to combat the conditions such as depression, anxiety, obsessive compulsive disorders, tremor and the like.

The subject compounds may be formulated into various pharmaceutical forms for administration purposes. Said pharmaceutical forms or compositions are deemed novel and consequently constitute another aspect of the present invention. Also the preparation of said compositions constitutes a further aspect of the present invention. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection.

For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deletorious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In view of the usefulness of the subject compounds in the treatment of neurotransmitter mediated diseases it is evident that the present invention provides a method of treating warm-blooded animals suffering from such diseases, said method comprising the systemic administration of a pharmaceutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof in admixture with a

pharmaceutical carrier. Those of skill in the treatment of diseases associated with neurotransmitters could easily determine the effective amount. In general it is contemplated that an effective amount would be from 0.01 mg/kg to 4 mg/kg body weight, preferably from 0.04 mg/kg to 2 mg/kg body weight.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore guidelines only and are not intended to limit the scope or use of the invention to any extent.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects. Unless otherwise stated all parts therein are by weight.

Experimental part

A. Preparation of intermediates

Example 1

a) To a stirred of mixture of 56 ml of 1,3-difluorobenzene, 130 g of aluminium chloride and 147 ml of dichloromethane, a solution of 95 g of 1-acetyl-4-piperidinecarbonyl chloride in 50 ml of dichloromethane was added dropwise while cooling. Upon completion, stirring was continued for 3 hours at room temperature. The reaction mixture was poured out into a mixture of crushed ice and hydrochloric acid. The product was extracted with dichloromethane. The organic layer was dried, filtered and evaporated, yielding 48 g (36%) of 1-acetyl-4-(2,4-difluorobenzoyl)piperidine as a residue (interm. 1).

b) 31.2 g of a dispersion of sodium hydride in mineral oil (50%) under a nitrogen atmosphere was washed twice with petroleum ether. There were added 230 ml of dimethyl sulfoxide. After stirring for 45 minutes at 70-75°C, the reaction mixture was cooled to a temperature of about 10°C. Then a suspension of 143 g of trimethylsulfoxonium iodide in 100 ml of dimethyl sulfoxide was added. The whole was stirred for 5 minutes and there was added a suspension of 135 g of intermediate (1) in 170 ml of tetrahydrofuran. The temperature was rised to 25-35°C, and the reaction mixture was

stirred for 2 hours at room temperature. The reaction mixture was poured out into crushed ice and the product was extracted with 2,2'-oxybispropane. The extract was stirred with activated charcoal, dried, filtered and evaporated, yielding 96g (68.3%) of 1-acetyl-4-[2-(2,4-difluorophenyl)oxiranyl]piperidine as an oily residue (interm. 2).

c) To a mixture of 96 g of intermediate (2) and 24.2 g of boron trifluoride etherate at room temperature were added 700 ml of benzene. After stirring for 45 minutes at reflux temperature, the reaction mixture was cooled and washed twice with 400 ml of water. The organic layer was separated and stirred with activated charcoal, dried, filtered and evaporated, yielding 80 g (83.6%) of 1-acetyl-α-(2,4-difluorophenyl)-4-piperidine-acetaldehyde (interm. 3).

d) 2.4 g of a dispersion of sodium hydride in mineral oil (50%) under a nitrogen atmosphere was washed twice with petroleum ether. There were added 60 ml of N,N-dimethylformamide. The whole was stirred at room temperature and a solution of 11.2 g of intermediate (3) in 40 ml of N,N-dimethylformamide was added dropwise. After stirring for 3 hours at 100-105°C, the reaction mixture was evaporated and the residue was stirred in water. The product was extracted with dichloromethane. The extract was separated, dried, filtered and evaporated. The residue was stirred in acetonitrile and mixed with activated charcoal. The whole was filtered and the filtrate was evaporated, yielding 9 g (86.1%) of 1-acetyl-4-(6-fluoro-3-benzofuranyl)piperidine (interm. 4).

e) A mixture of 63 g intermediate (4) in 630 ml of hydrochloric acid 6N was stirred for 3 hours at reflux temperature. After cooling, the reaction mixture was washed with methylbenzene. The mixture was stirred at room temperature and a precipitate was formed. The precipitate was filtered off and washed with some 2-propanone and dried, yielding 34 g (55.4%) of product (fraction 1). The filtrate was evaporated and the residual oil was dissolved in 2-propanone. This solution was stirred at room temperature and a precipitate was formed, yielding 9g (15%) of product (fraction 2). Total yield: 43g (70.4%) of 4-(6-fluoro-3-benzofuranyl)piperidine hydrochloride; mp. 238.1°C; (interm. 5).

B. Preparation of final compounds

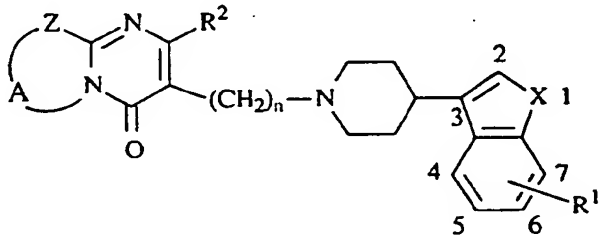
Example 2

A mixture of 3.8 g of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 3.8 g of intermediate (5), 10 g of sodium carbonate and a few crystals of potassium iodide in 180 ml of 4-methyl-2-pentanone was stirred overnight at reflux temperature. After cooling, the reaction mixture was poured out into water. The separated organic layer was dried, filtered and evaporated. The residue was purified by column chromato-

graphy over silica gel (eluent : CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 3.8 g (62.5%) of 3-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one; mp. 159.8°C; (comp. 1).

In this manner were prepared :

Table 1



Co. No.	-Z-A-	R^2	n	X	R^1	mp.
1	-CH=CH-CH=CH-	CH_3	2	O	6-F	159.8°C
2	$-(CH_2)_4-$	CH_3	2	O	6-F	164.7°C
3	$-S-(CH_2)_2-$	CH_3	2	O	6-F	192.5°C
4	-S-CH=CH-	CH_3	2	O	6-F	161.1°C
5	$-CH=C(CH_3)-O-$	CH_3	2	O	6-F	150.8°C
6	-S-CH=CH-	CH_3	2	S	H	135.8°C
7	$-(CH_2)_4-$	CH_3	2	S	H	122.8°C
8	$-C(CH_3)=CH-CH=CH-$	CH_3	2	S	H	161.3°C
9	$-S-CH=C(CH_3)-$	CH_3	3	O	6-F	216.9°C *
10	$-S-(CH_2)_3-$	CH_3	3	O	6-F	198.9°C *
11	$-S-(CH_2)_2-$	CH_3	3	O	6-F	204.1°C *
12	$-C(=CH-C_6H_5)-(CH_2)_3-$	CH_3	2	O	6-F	135.9°C (E)
13	-S-CH=CH-	CH_3	3	O	6-F	186.9°C *
14	$-C(CH_3)=CH-CH=CH-$	CH_3	3	O	6-F	104.7°C

Co. No.	-Z-A-	R^2	n	X	R^1	mp.
15	-C[=CH-(4-F-C_6H_4)]-(CH_2)$_3$-	CH_3	2	O	6-F	189.4°C (E)
16	-CH[-CH_2-(4-F-C_6H_4)]-(CH_2)$_3$-	CH_3	2	O	6-F	185.8°C
17	-$(CH)_4$-	-CH_2-C_6H_5	2	O	6-F	158.7°C

* = (E)-2-butenedioate (1:1)

C. Pharmacological example

Example 3 : Reserpine Tremor Test

Female Wistar rats weighing 200-220 g were used. These test animals were food deprived for 24 hours. Said rats were pretreated orally (po) or subcutaneously (sc) with a test compound at 90 minutes before testing. This pretreatment was followed by an intravenous injection of 2 mg/kg reserpine at 60 minutes before testing. Two control groups of 20 rats each were included in the experiment. The first control group consisted of rats that were only treated with a saline solution and the second control group consisted of animals which only received a saline reserpine solution.

At the start of the test, the rats were individually placed in specially designed test cages and tremor activity was measured continuously during a 15-min test session.

These test cages consisted of a plexiglass chamber. The floor of the test cage consisted of a plexiglass plate which was centered underneath the cage. The cage did not support onto this floor plate. The floor plate rested at its four corners on a rubber point of support. Two pieces of piezo-film were tied up next to each other underneath the middle of the floor plate. Said piezo-films were connected to an amplifier. The test cage was situated in a sound and light attenuating out box, being constantly illuminated and air-ventilated.

The piezo-electric response, produced by deformation of the cage floor was amplified by an individual amplifier for each piezo-film separately. The sum of these signals was observed by a noise detection system which prevented further transmission if the signal was below the selected noise level of 100 mVolt. The tremor count in these experiments represented the appearance of 10 successive electrical signals that, after having been amplified and filtered, all exceeded a trigger level of 100 mVolt and differed no more than 400 mVolt from each other. The average activity of the control group that only received a saline solution was about 34 and the tremor activity of the reserpine treated control group was about 152 counts. On this basis, a compound was deemed active at a certain dose if the tremor activity is below 35 counts and deemed inactive when the tremor activity was above said count level. The activity of compounds are shown in Table 2.

Table 2

Co No	route	dose (mg/kg)	rats showing a tremor activity below 35 counts	rats tested
1	sc	2.5	3	3
2	sc	2.5	2	2
4	sc	2.5	3	3
5	sc	2.5	2	2
9	po	2.5	2	2

D. Composition examples

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 4 : ORAL DROPS

500 Grams of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60–80°C. After cooling to 30–40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 grams of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of A.I.. The resulting solution was filled into suitable containers.

Example 5 : ORAL SOLUTION

9 Grams of methyl 4-hydroxybenzoate and 1 gram of propyl 4-hydroxybenzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 grams of 2,3-dihydroxybutanedioic acid and thereafter 20 grams of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 Grams of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example 6 : CAPSULES

20 Grams of the A.I., 6 grams sodium lauryl sulfate, 56 grams starch, 56 grams lactose, 0.8 grams colloidal silicon dioxide, and 1.2 grams magnesium stearate were vigorously

stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, comprising each 20 mg of the active ingredient.

Example 7 : FILM-COATED TABLETS

Preparation of tablet core

A mixture of 100 grams of the A.I., 570 grams lactose and 200 grams starch was mixed well and thereafter humidified with a solution of 5 grams sodium dodecyl sulfate and 10 grams polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 grams microcrystalline cellulose and 15 grams hydrogenated vegetable oil. The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

Coating

To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 grams of magnesium octadecanoate, 5 grams of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 8 : INJECTABLE SOLUTION

1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 grams lactic acid, 0.05 grams propylene glycol and 4 grams of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration and filled in sterile containers.

Example 9 : SUPPOSITORIES

3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 Grams surfactant and triglycerides q.s. ad 300 grams were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg/ml of the A.I.

Example 10 : INJECTABLE SOLUTION

60 Grams of A.I. and 12 grams of benzylalcohol were mixed well and sesame oil was added q.s. ad 1 l, giving a solution comprising 60 mg/ml of A.I. The solution was sterilized and filled in sterile containers.

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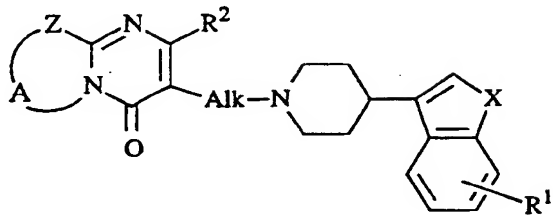
Claims

1. A compound having the formula



(I),

a pharmaceutically acceptable acid addition salt thereof and a stereochemically isomeric form thereof, wherein

X is oxygen or sulphur;

R^1 is hydrogen or halo;

R^2 is hydrogen, C_{1-4}alkyl, phenylmethyl or halophenylmethyl;

Alk is C_{1-4}alkanediyl;

-Z-A- is a bivalent radical selected from the group consisting of -S-CH_2-CH_2-, -S-CH_2-CH_2-CH_2-, -S-CH=CH-, -CH=CH-CH=CH-, -C(=CHR^3)-CH_2-CH_2-CH_2-, -CH=CH-O-, -CHR^4-CH_2-CH_2-, -CHR^4-CH_2-CH_2-CH_2-, -CHR^4-CH_2-CH_2-CH_2-CH_2-; wherein in said bivalent radicals one hydrogen may be replaced by C_{1-4}alkyl;

R^3 is phenyl or halophenyl; and

each R^4 independently represents hydrogen, hydroxy, phenylmethyl or halophenylmethyl.

2. A compound according to claim 1, wherein R^1 is hydrogen or fluoro, R^2 is C_{1-4}alkyl or phenylmethyl, R^3 is phenyl or 4-fluorophenyl, R^4 is hydrogen, phenylmethyl or 4-fluoromethylphenyl and Alk represents C_{2-3}alkanediyl.

3. A compound according to claim 1 or 2, wherein X is oxygen, Alk is 1,2-ethanediyl or 1,3-propanediyl and R^4 is hydrogen.

4. A compound according to claim 1 or 2, wherein X is sulfur, Alk is 1,2-ethanediyl or 1,3-propanediyl and R^4 is hydrogen.

5. A compound according to claim 1 or 2, wherein-Z-A- is a bivalent radical of formula -S-CH_2-CH_2-, -S-CH=CH-, -S-CH_2-CH_2-CH_2-, -CH=CH-CH=CH-, -CH_2-CH_2-CH_2-CH_2- or -CH=C(CH_3)-O-.

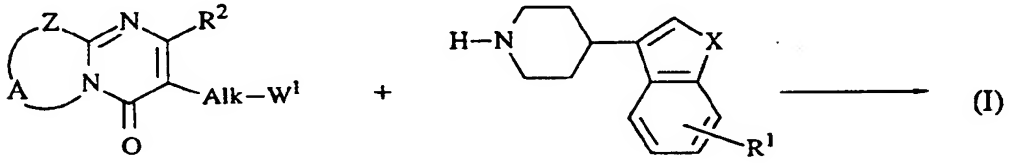
6. A compound according to claim 1, wherein the compound is 3-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one, 6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo-[3,2-a]pyrimidin-5-one or a pharmaceutically acceptable acid addition salt thereof.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as an active ingredient a therapeutically effective amount of a compound as claimed in any of claims 1 to 6.

8. A process of preparing a composition as claimed in claim 7 characterized in that a therapeutically active amount of a compound as claimed in any of claims 1 to 5 is intimately mixed with a pharmaceutically acceptable carrier.

9. A compound as claimed in any of claims 1 to 6 for use as a medicine.

10. A process for preparing an compound as claimed in claim 1, characterized by N-alkylating an intermediate of formula (II) with an intermediate of formula (III), wherein W^1 represents a reactive leaving group,



(III) (II) (I)

and optionally converting the compounds of formula (I) into each other by a functional group transformation reaction; and, if desired, converting a compound of formula (I) into a therapeutically active non-toxic acid addition salt, or conversely, converting an acid addition salt into a free base form with alkali; and/ or preparing stereochemically isomeric forms thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/01776

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D471/04; C07D513/04; C07D498/04; A61K31/505
//(C07D471/04,239:00,221:00)(C07D513/04,277:00,239:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
Y	EP,A,0 378 255 (JANSSEN PHARMACEUTICA) 18 July 1990 cited in the application see claims 1,7	1,7
Y	EP,A,0 196 132 (JANSSEN PHARMACEUTICA) 1 October 1986 see claims 1,7	1,7
Y	EP,A,0 070 053 (JANSSEN PHARMACEUTICA) 19 January 1983 see claims 1,7	1,7
Y	EP,A,0 037 265 (JANSSEN PHARMACEUTICA) 7 October 1981 see claims 1,5,10	1,7

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21 SEPTEMBER 1993	- 4. 10. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VOYIAZOGLOU D.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9301776
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 21/09/93
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